Attorney Docket No. 119027-00901
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent of:
Böttcher *et al.*

Patent No.: 5,532,241

Issued: July 2, 1996

For: PIPERIDINES AND PIPERAZINES

Mail Stop: Hatch-Waxman PTE
U.S. Patent and Trademark Office
Office of Patent Legal Administration
Room MDW7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

INFORMATION DISCLOSURE STATEMENT

Dear Madam:

In accordance with the duty of disclosure as described in 37 C.F.R. §1.765 and acknowledged under 37 C.F.R. §1.740(13), Marketing Applicant, Trovis Pharmaceuticals LLC, as agent for Applicant, Merck Patent GmbH, wishes to formally inform the Office that two patent term extension applications have been filed concurrently with respect to the regulatory review period for VIIBRYD™ (vilazodone hydrochloride) Tablets. Such patent term extension applications are now pending before the Office and pertain to U.S. Patent Nos. 5,532,241 (*i.e.*, the present application) and 7,834,020. It is requested that the Office examine these applications concurrently so that a meaningful election can be made upon the receipt of a Notice of Final Determination and Requirement of Election as to which patent to ultimately extend in accordance with 37 C.F.R. §1.785.

It is believed that no fee is required for the filing of this Information Disclosure Statement. However, should a fee be required with the filing of this paper (or with any paper hereafter filed in this patent term extension application by this firm), the Director is hereby

authorized to charge our Deposit Account No. 50-4876, under Docket No. 119027-00901. A duplicate copy of this paper is enclosed.

Dated: March 17, 2011

Respectfully submitted,

By _____

Scott A.M. Chambers, Ph.D.
Registration No.: 37,573
PATTON BOGGS LLP
8484 Westpark Drive, 9th Floor
McLean, Virginia 22102
(703) 744-8085
(703-744-8001 (Fax)

Attorney Docket No. 119027-00901
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Alexandria, VA 22314

TRANSMITTAL LETTER

Dear Madam:

Enclosed are the following items for filing in connection with the above-referenced Patent:

1. Fee Transmittal;

2. Request for Extension of Patent Term under 35 U.S.C. §156 (original plus two copies) together with Exhibits 1-11 (original plus two copies);

3. Information Disclosure Statement (original plus one copy);

4. Credit Card Payment Form; and

5. Return receipt postcard.

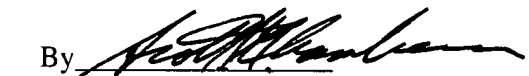
Payment is submitted by Credit Card in the amount of $1,120.00 covering the fee set forth in 37 CFR 1.20(j) (1). The Director is hereby authorized to charge any deficiency in the

fees filed, asserted to be filed or which should have been filed herewith (or with any other paper hereafter filed in this application by this firm) to our Deposit Account No. 50-4876, under Docket No. 119025-00901. A duplicate copy of this paper is enclosed.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. §1.136(a), and any fees required therefore (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 50-4876.

Dated: March 17, 2011

Respectfully submitted,

By 

Scott A.M. Chambers, Ph.D.
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PTO/SB/17 (10-08)
Approved for use through 09/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no person are required to respond to a collection of information unless it displays a valid OMB control number

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2009

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,120.00

Complete if Known	
Application Number	Patent No. 5532241
Filing Date	Issued: July 2, 1996
First Named Inventor	Henning Bottcher
Examiner Name	N/A
Art Unit	N/A
Attorney Docket No.	119027-00901

METHOD OF PAYMENT (check all that apply)

☐ Check ☒ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☐ Deposit Account Deposit Account Number: 50-4876 Deposit Account Name: McCarter & English LLP

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
Application Type	**Fee ($)**	**Small Entity Fee ($)**	**Fee ($)**	**Small Entity Fee ($)**	**Fee ($)**	**Small Entity Fee ($)**	**Fees Paid ($)**
Utility	330	165	540	270	220	110	
Design	220	110	100	50	140	70	
Plant	220	110	330	165	170	85	
Reissue	330	165	540	270	650	325	
Provisional	220	110	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	**Fee ($)**	**Small Entity Fee ($)**
Each claim over 20 (including Reissues)	52	26
Each independent claim over 3 (including Reissues)	220	110
Multiple dependent claims	390	195

Total Claims	**Extra Claims**	**Fee ($)**	**Fee Paid ($)**
_____ - 20 or HP =	_____	x _____	= _____

HP = highest number of total claims paid for, if greater than 20.

Multiple Dependent Claims	
Fee ($)	**Fee Paid ($)**
_____	_____

Indep. Claims	**Extra Claims**		**Fee Paid ($)**
_____ - 3 or HP =	_____	x _____	= _____

HP = highest number of independent claims paid for, if greater than 3.

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $270 ($135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

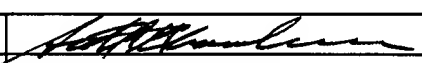
Total Sheets	**Extra Sheets**	**Number of each additional 50 or fraction thereof**	**Fee ($)**	**Fee Paid ($)**
_____ - 100 =	_____	/50 = _____ (round up to a whole number) x	_____	= _____

4. OTHER FEE(S) **Fees Paid ($)**

Non-English Specification, $130 fee (no small entity discount) _____

Other (e.g., late filing surcharge): 1457 Extension of term patent $1,120.00

SUBMITTED BY

Signature		Registration No. (Attorney/Agent)	37,573	Telephone	(703) 744-8085
Name (Print/Type)	Scott A.M. Chambers, Ph.D.			Date	March 17, 2011

RECEIVED
MAR 17 2011
PATENT EXTENSION
OPLA

3725343

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent of:
Böttcher *et al.*

Patent No.: 5,532,241

Issued: July 2, 1996

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REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Sir:

Pursuant to 35 U.S.C. §156 and 37 C.F.R. §§1.710-1.791, Applicant, Merck Patent GmbH, the address of which is Frankfurter Strasse 250, 64293 Darmstadt, Germany, represents that it is the owner and assignee of the entire interest in and to Letters Patent of the United States No. 5,532,241 (attached as Exhibit 1, "the '241 patent") granted to Henning Böttcher, Christoph Seyfried, Gerd Bartoszyk and Hartmut Greiner on the 2nd day of July, 1996, for "Piperidines and Piperazines," by virtue of an assignment from Henning Böttcher, Christoph Seyfried, Gerd Bartoszyk and Hartmut Greiner to Merck Patent GmbH, recorded on November 14, 1994 at Reel 007210, Frame 0397 (attached as Exhibit 2). The '241 patent matured from United States Patent Application No. 08/314,734 (hereinafter "the '734 application"), filed September 29, 1994.

The approved product that is relevant to this application is VIIBRYD™ (vilazodone hydrochloride) Tablets, referred to herein as "VIIBRYD" or "Approved Product."

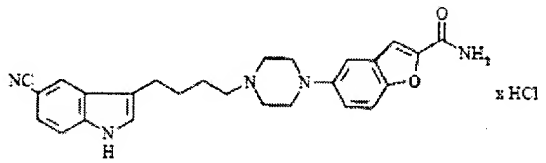
The Marketing Applicant for VIIBRYD is Trovis Pharmaceuticals LLC, a subsidiary of Clinical Data, Inc., of One Gateway Center, Suite 702, Newton, MA 02458. A letter on behalf of the Marketing Applicant authorizing the patent owner to rely upon the activities of the Marketing Applicant, its predecessors and affiliates, is attached as Exhibit 3.

The following information is submitted by Trovis Pharmaceuticals LLC through its duly authorized attorney, on behalf of Applicant (Power of Attorney attached as Exhibit 4), in accordance with 35 U.S.C. §156(d) and the rules for extension of patent term issued by the USPTO at 37 C.F.R. Subpart F, §§1.710 to 1.791 and follows the numerical format set forth in 37 C.F.R. §1.740.

(1) A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT AS BY APPROPRIATE CHEMICAL AND GENERIC NAME, PHYSICAL STRUCTURE OR CHARACTERISTICS:

The approved product is VIIBRYD Tablets, a formulation with 10, 20 or 40 mg of active ingredient polymorph Form IV vilazodone hydrochloride (HCl). VIIBRYD has been approved for the treatment of major depressive disorder (MDD) (The insert for the approved product is attached as Exhibit 5).

The chemical name of vilazodone hydrochloride is 2-benzofurancarboxamide, 5-[4-[4-(5-cyano-1*H*-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride, with the chemical structure:



(2) A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED:

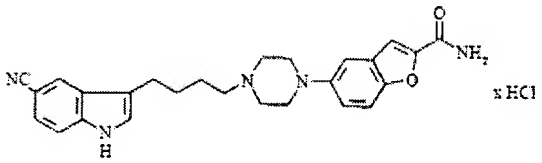
The regulatory review occurred under Section 505(b) of Federal Food, Drug, and Cosmetic Act ("FFDCA") (21 U.S.C. §355(b) and §355(i)). Section 505(b) provides for the submission and approval of new drug applications ("NDAs").

(3) AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE UNDER THE PROVISION OF LAW UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED:

The Approved Product received permission for commercial marketing or use by the Food and Drug Administration ("FDA") pursuant to Section 505(b) of the FFDCA in a letter dated January 21, 2011. A copy of the approval letter is attached as Exhibit 6.

(4) IN THE CASE OF A DRUG PRODUCT, AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FFDCA, THE PUBLIC HEALTH SERVICE ACT, OR THE VIRUS-SERUM-TOXIN ACT OR A STATEMENT OF WHEN THE ACTIVE INGREDIENT WAS APPROVED FOR COMMERCIAL MARKETING OR USE (EITHER ALONE OR IN COMBINATION WITH OTHER ACTIVE INGREDIENTS), THE USE FOR WHICH IT WAS APPROVED AND THE PROVISION OF LAW UNDER WHICH IT WAS APPROVED: (37 C.F.R. §1.740(a)(4))

VIIBRYD has been approved under section 505(b) of the FFDCA for treatment of major depressive disorder (MDD). The active ingredient in VIIBRYD is vilazodone hydrochloride, with the chemical structure:



Neither vilazodone hydrochloride, nor any salt or ester of that active ingredient, have been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act, and the FDA has determined that VIIBRYD is a New Molecular Entity.

(5) A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE 60 DAY PERIOD PERMITTED FOR SUBMISSION PURSUANT TO SECTION 1.720(f) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED.

This Application is timely filed, pursuant to 35 U.S.C. §156(d)(1), within the permitted sixty (60) day period that began on January 21, 2011 when the product received permission under 21 U.S.C. §355(b) and that will expire on March 22, 2011. Applicant understands that, pursuant to 37 C.F.R. §1.720(f), the USPTO may deem this period to expire one day earlier, on March 21, 2011.

(6) A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT BY THE NAME OF THE INVENTOR, THE PATENT NUMBER, THE DATE OF ISSUE AND THE DATE OF EXPIRATION:

United States Patent No.	5,532,241
Inventors:	Böttcher *et al.*
Date of Issue:	July 2, 1996
Expiration Date:	September 29, 2014

The Expiration of the '241 patent is September 29, 2014 based on the following: The patent application (the '734 application) that issued as the '241 patent was filed on September 29, 1994. Because the '734 application was filed prior to June 8, 1995, the expiration date of the '241 patent is the greater of either seventeen (17) years from the issue date of the '241 patent (*e.g.*, July 2, 2013) or twenty (20) years from the filing date of the '734 application (*e.g.*, September 29, 2014). The term expiring twenty (20) years from the filing date of the '734 application is the greater of the two terms. Therefore, the Expiration Date of the '241 patent is September 29, 2014.

(7) A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT, INCLUDING THE ENTIRE SPECIFICATION (INCLUDING CLAIMS) AND DRAWINGS:

A complete copy of U.S. Patent No. 5,532,241 is attached as Exhibit 1.

(8) A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR RE-EXAMINATION CERTIFICATE ISSUED IN THE U.S. PATENT:

U.S. Patent No. 5,532,241 is not subject to any disclaimer.

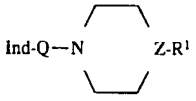
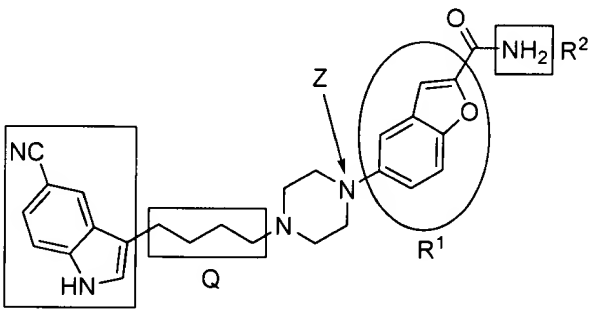
U.S. Patent No. 5,532,241 has not been re-examined, and so no re-examination certificate has been issued.

A Certificate of Correction for U.S. Patent No. 5,532,241 was signed and sealed on November 10, 2009. A copy of the Certificate of Correction is attached as Exhibit 7.

The fourth, eighth and twelve year maintenance fees for U.S. Patent No. 5,532,241 have been paid, as shown by the Patent Bibliographic Data Sheet dated February 8, 2011 (attached as Exhibit 8). Accordingly, there are no unpaid maintenance fees for this patent.

(9) A STATEMENT THAT THE PATENT CLAIMS THE APPROVED PRODUCT, OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT CLAIM AND DEMONSTRATES THE MANNER IN WHICH AT LEAST ONE SUCH PATENT CLAIM READS ON THE APPROVED PRODUCT OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT:

U.S. Patent No. 5,532,241 claims the Approved Product. Specifically, claims 1-4, 7, 8, 10, 11, 16 and 17 read on the Approved Product. Pursuant to 37 C.F.R. §1.740(a)(9), a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on the approved product is set forth below.

CLAIMS	ELEMENTS
1. A compound according to formula I  wherein Ind is unsubstituted indol-3-yl, indol-3-yl monosubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2, or indol-3-yl polysubstituted by OH, OA, CN, Hal, COR^2, CH_2R^2 or combinations thereof;R^1 is benzofuran-5-yl, chroman-4-on-6-yl, 3-chromen-6-yl or chromen-4-on-6-yl, which in each case is unsubstituted or monosubstituted by CN, CH_2OH, CH_2OA or COR^2; Q is C_mH_{2m}; Z is N; A is alkyl having 1-6 C atoms; Hal is F, Cl, Br or I; R^2 is OH, OA, NH_2, NHA or NA_2; and m is 2, 3, or 4; or a physiologically acceptable salt thereof.	The active ingredient in VIIBRYD is vilazodone HCl which has the structure:  Ind having ▪ an indol-3-yl moiety monosubstituted with a cyano moiety (*i.e.*, Ind is indol-3-yl monosubstituted by CN) ▪ an n-butyl chain (*i.e.*, Q is C_mH_{2m}, m is 4) ▪ a piperazine moiety (*i.e.*, Z is N) ▪ a benzofuran-5-yl moiety that is monosubstituted with an amido moiety (*i.e.*, R^1 is benzofuran-5-yl monosubstituted by COR^2, R^2 is NH_2).
2. A compound according to claim 1, wherein said compound is: (a) 1-[4-(5-methoxyindol-3-yl)butyl]-4-(2-hydroxymethylbenzofuran-5-yl)piperazine or a physiologically acceptable salt thereof; (b) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-ethoxycarbonyl-benzofuran-5-yl)piperazine or a physiologically acceptable salt thereof; or (c) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoylbenzofuran-5-yl)piperazine or a physiologically acceptable salt thereof.	An alternative chemical name for vilazodone is 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoylbenzofuran-5-yl)piperazine.
3. A compound according to claim 1, wherein Ind is unsubstituted indol-3-yl, indol-3-yl monosubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2, or indol-3-yl disubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2.	The indol-3-yl moiety of vilazodone is monosubstituted with a cyano moiety (*i.e.*, Ind is indol-3-yl monosubstituted by CN).
4. A compound according to claim 1, wherein Ind is indol-3-yl monosubstituted in the 5-position by OH, OA, CN, Hal, COR^2 or CH_2R^2.	The indol-3-yl moiety of vilazodone is monosubstituted at the 5-position with a cyano moiety (*i.e.*, Ind is indol-3-yl monosubstituted in the 5-position by CN).

7. A compound according to claim 1, wherein R^1 is benzofuran-5-yl, or chroman-4-on-6-yl which, in each case is unsubstituted or monosubstituted by $-CH_2OH$, $-CONH_2$, $-CO_2A$ or $-CO_2NHA$.	The benzofuran-5-yl moiety of vilazodone is monosubstituted with $-CONH_2$ (*i.e.*, R^1 is benzofuran-5-yl monosubstituted by $-CONH_2$).
8. A compound according to claim 1, wherein Q is $-(CH_2)_4-$.	The alkyl linker between the indol-3-yl moiety and the piperazine moiety of vilazodone is an n-butyl moiety (*i.e.*, Q is $-(CH_2)_4-$).
10. A compound according to claim 1, wherein Ind is indol-3-yl substituted in the 5-position by $CONH_2$ or CN.	The indol-3-yl moiety of vilazodone is monosubstituted at the 5-position with a cyano moiety (*i.e.*, Ind is indol-3-yl substituted in the 5-position by CN).
11. A compound according to claim 1, wherein R^1 is unsubstituted benzofuran-5-yl or benzofuran-5-yl substituted by CN, CH_2OH, CH_2OA or COR^2.	The benzofuran-5-yl moiety of vilazodone is substituted with $-COR^2$, wherein R^2 is NH_2 (*i.e.*, R^1 is benzofuran-5-yl substituted by COR^2).
16. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.	The Approved Product is a pharmaceutical composition comprising vilazodone hydrochloride and a pharmaceutically acceptable carrier.
17. A composition according to claim 16, wherein said compound is present in an amount of 0.2-500 mg.	The Approved Product comprises 10, 20 or 40 mg of vilazodone hydrochloride.

(10) A STATEMENT BEGINNING ON A NEW PAGE OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. §156(G) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE, AS APPROPRIATE, TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD AS FOLLOWS:

(i) FOR A PATENT CLAIMING A HUMAN DRUG, ANTIBIOTIC OR HUMAN BIOLOGICAL PRODUCT, THE EFFECTIVE DATE OF THE INVESTIGATIONAL NEW DRUG APPLICATION (IND) AND THE IND NUMBER; THE DATE ON WHICH A NEW DRUG APPLICATION (NDA) OR A PRODUCT LICENSE APPLICATION (PLA) WAS INITIALLY SUBMITTED AND THE NDA OR PLA NUMBER; AND THE DATE ON WHICH THE NDA WAS APPROVED OR THE PRODUCT LICENSE ISSUED:

An original investigational new drug application ("IND") was filed on November 21, 1997 and assigned IND No. 54,613. A copy of the letter acknowledging receipt of the IND is attached as Exhibit 9. The IND became effective December 24, 1997 (*e.g.*, 30 days from receipt of the IND).

A new drug application ("NDA") was submitted on March 22, 2010 and acknowledged as received on March 22, 2010, in a letter from the FDA dated March 24, 2010 (attached as Exhibit 10). The NDA number assigned to the application for vilazodone hydrochloride was 22-567. Accordingly, the NDA was initially submitted on March 22, 2010. The NDA was approved on January 21, 2011 (Approval Letter attached as Exhibit 6).

(11) A BRIEF DESCRIPTION BEGINNING ON A NEW PAGE OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY THE MARKETING APPLICANT, DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES:

In accordance with 37 C.F.R. §1.740(a)(11), a list of significant activities undertaken by the Marketing Applicant, its predecessors, and affiliates, in IND No. 54,613 and NDA No. 22-567 during the applicable regulatory review period with respect to the Approved Product is attached as Exhibit 11.

(12) A STATEMENT BEGINNING ON A NEW PAGE THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR THE EXTENSION AND A STATEMENT AS TO THE LENGTH OF THE EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED:

(a) Statement of the eligibility of U.S. Patent No. 5,532,241 for extension under 35 U.S.C. § 156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. §156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product using the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) Pursuant to 35 U.S.C. §154, the term of U.S. Patent No. 5,532,241 is currently set to expire on September 29, 2014, for reasons discussed above. This application is, therefore, being submitted prior to the expiration of the term of U.S. Patent No. 5,532,241.

(2) The term of this patent has never been extended under 35 U.S.C. §156(e)(1).

(3) This application is being submitted by Trovis Pharmaceuticals LLC, as agent for Applicant, Merck Patent GmbH, the owners of record of U.S. Patent No. 5,532,241 (see Exhibit 3 and Exhibit 4). Merck Patent GmbH is this owner of record by virtue of the duly recorded assignments discussed above (see Exhibit 2). This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty (60) day period beginning on January 21, 2011, the date the product received permission for marketing under Section 505(b) of the FFDCA (21 U.S.C. §355), and ending on March 22, 2011. Moreover, this application contains the information required under 35 U.S.C. §156(d).

(4) As evidenced by the January 21, 2011 letter from the FDA to Trovis Pharmaceuticals LLC, attached as Exhibit 6, the Approved Product was subject to a regulatory review period under Section 505(b) of the FFDCA before its commercial marketing or use.

(5) The permission for the commercial marketing of the VIIBRYD product is the first permitted commercial marketing and use under Section 505 of the FFDCA (21 U.S.C. §355) of the product, as defined in 35 U.S.C. §156(f) (see Section 4, above).

(b) Statement as to length of extension claimed.

The term of U.S. Patent No. 5,532,241, currently expiring September 29, 2014 should be extended for five (5) years, or to September 29, 2019, in accordance with 35 U.S.C. §156.

As set forth in 35 U.S.C. §156(g)(1), the regulatory review period equals the sum of the number of days in the period beginning on the effective date of IND No. 54,613, which is December 24, 1997, and ending on the date of submission of NDA No. 22-567, which is March 22, 2010 (*e.g.*, the "Testing Phase"), and the number of days in the period beginning on the date of submission of NDA No. 22-567, which is March 22, 2010, and ending on the date of NDA approval, which is January 21, 2011 (*e.g.*, the "Approval Phase"). Including the starting and the ending date, this Testing Phase is a period of four-thousand, four-hundred, seventy-two (4,472) days as calculated at http://www.timeanddate.com/date/duration.html. This is added to the Approval Phase, which--including the starting and the ending date--is a period of three-hundred, six (306) days, as calculated at http://www.timeanddate.com/date/duration.html. The sum of these two periods is the regulatory review period which equals four-thousand, seven-hundred, seventy-eight (4,778) days.

Pursuant to 37 C.F.R. §1.775(d), the term of the patent as extended is determined by subtracting from the four-thousand, seven-hundred, seventy-eight (4,778) day regulatory review period the following:

(i) zero (0) days, which is the number of days in the IND and NDA periods on or before the issuance of U.S. Patent No. 5,532,241 on July 2, 1996; and

(ii) two-thousand, two-hundred, thirty-six (2,236) dayswhich is one-half the number of days in the Testing Phase, as provided by 37 C.F.R. 1.775(d)(1)(iii).

From the foregoing calculation, an extension of two-thousand, five-hundred, forty-two (2,542) days results (*e.g.*, four-thousand, seven-hundred, seventy-eight(4,778) days minus the two-thousand, two-hundred, thirty-six (2,236) days). This length of an extension would provide a new expiration date for U.S. Patent No. 5,532,241 of September 14, 2021. However, this extension period is subject to two further potential limitations under 35 U.S.C. §156.

First, under 35 U.S.C. §156(g)(6)(A), a maximum extension of five (5) years is permitted. In this case, since the current expiry date of U.S. Patent No. 5,532,241 is September 29, 2014, no patent term extension may extend the term of this patent beyond September 29, 2019. This provision thus limits the patent term extension available to the '241 patent to five (5) years, or to September 29, 2019.

Second, under 35 U.S.C. §156(c)(3), if the calculated extension period would lead to a patent term that would result in a patent term exceeding fourteen (14) years after the approval date (*e.g.*, a patent term expiring after January 21, 2026), the period of extension would be limited so that this period does not exceed fourteen (14) years. In this case, this provision does not operate to limit the possible extension available to U.S. Patent No. 5,532,241.

Accordingly, U.S. Patent No. 5,532,241 is eligible for a patent term extension of five (5) years.

(13) A STATEMENT THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE TO THE DIRECTOR OF THE UNITED STATES PATENTS AND TRADEMARK OFFICE AND THE SECRETARY OF HEALTH AND HUMAN SERVICES ANY INFORMATION WHICH IS MATERIAL TO THE DETERMINATION OF ENTITLEMENT TO THE EXTENSION SOUGHT (SEE 37 C.F.R. §1.765):

Merck Patent GmbH and Trovis Pharmaceuticals LLC acknowledge a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) THE PRESCRIBED FEE FOR RECEIVING AND ACTING UPON THE APPLICATION FOR EXTENSION (SEE 37 C.F.R. §1.20(j)):

Payment is submitted by Credit Card in the amount of $1,120.00 covering the fee set forth in 37 CFR 1.20(j) (1). The Director is hereby authorized to charge our Deposit Account No. 50-4876, under Docket No. 119027-00901, for any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm), to prevent this application from being inadvertently abandoned.

(15) THE NAME, ADDRESS AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THE APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED:

Danielle L. Herritt
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265 Franklin Street
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Pursuant to 37 C.F.R. § 1.740(b), this Request for Extension of Patent Term under 35 U.S.C. § 156, including Exhibits 1-11, is accompanied by two additional copies, for a total submission of three copies.

Dated: March 17, 2011

Respectfully submitted,

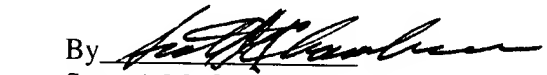
By 
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Exhibit List for Application for PTE for U.S. Patent No. 5,532,241

Exhibit 1:	U.S. Patent No. 5,532,241
Exhibit 2:	Executed Assignment
Exhibit 3:	Letter on Behalf of the Marketing Applicant Authorizing the Patent Owner to Rely upon the Activities of the Marketing Applicant
Exhibit 4:	Power of Attorney
Exhibit 5:	Approved Label
Exhibit 6:	NDA Approval Letter
Exhibit 7:	Certificate of Correction
Exhibit 8:	Patent Bibliographic Data
Exhibit 9:	Letter Acknowledging Receipt of the IND
Exhibit 10:	Letter Acknowledging Receipt of NDA
Exhibit 11:	List of Significant Activities Undertaken during Regulatory Review Period

EXHIBIT 1

U.S. Patent No. 5,532,241

US005532241A

United States Patent [19]

Böttcher et al.

[11] **Patent Number: 5,532,241**

[45] **Date of Patent: Jul. 2, 1996**

[54] **PIPERIDINES AND PIPERAZINES**

[75] Inventors: **Henning Böttcher**, Darmstadt; **Christoph Seyfried**, Seeheim-Jugenheim; **Gerd Bartoszyk**; **Hartmut Greiner**, both of Darmstadt, all of Germany

[73] Assignee: **Merck Patent Gesellschaft mit beschrankter Haftung**, Darmstadt, Germany

[21] Appl. No.: **314,734**

[22] Filed: **Sep. 29, 1994**

[30] **Foreign Application Priority Data**

Sep. 30, 1993 [DE] Germany 43 33 254.4

[51] **Int. Cl.**[6] **A61K 31/495**; A61K 31/445; C07D 405/10

[52] **U.S. Cl.** **514/254**; 544/373; 546/201; 514/323

[58] **Field of Search** 544/373; 514/254

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,002,948	3/1991	Perregaard et al.	544/373
5,242,925	9/1993	Böttcher et al.	514/254
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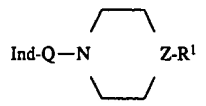
94/13659	6/1994	WIPO .

Primary Examiner—Emily Bernhardt
Attorney, Agent, or Firm—Millen, White, Zelano & Branigan

[57] **ABSTRACT**

Piperidine and piperazine derivatives of the formula I



I

wherein

Ind is an indol-3-yl radical which is unsubstituted or mono- or polysubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2,

R^1 is benzofuran-5-yl or 2,3-dihydrobenzofuran-5-yl, chroman-6-yl, chroman-4-on-6-yl, 3-chromen-6-yl or chromen-4-on-6-yl, which is unsubstituted or monosubstituted by CN, CH_2OH, CH_2OA or COR^2,

Q is C_mH_{2m},

N or CR^3,

A is alkyl having 1–6 C atoms,

Hal is F, Cl, Br or I,

R^2 is OH, OA, NH_2, NHA or NA_2,

$R^3$is H, OH or OA and

m is 2, 3 or 4,

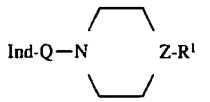
and their physiologically acceptable salts, are active on the central nervous system.

17 Claims, No Drawings

PIPERIDINES AND PIPERAZINES

SUMMARY OF THE INVENTION

The invention relates to novel piperidine and piperazine derivatives of the formula I



I

wherein

Ind is an indol-3-yl radical which is unsubstituted or mono- or polysubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2,

R^1 is benzofuran-5-yl or 2,3-dihydrobenzofuran-5-yl, chroman-6-yl, chroman-4-on-6-yl, 3-chromen-6-yl or chromen-4-on-6-yl, which is unsubstituted or monosubstituted by CN, CH_2OH, CH_2OA or COR^2,

Q is C_mH_{2m},

Z is N or CR^3,

A is alkyl having 1–6 C atoms,

Hal is F, Cl, Br or I,

R^2 is OH, OA, NH_2, NHA or NA_2,

R^3 is H, OH or OA and

m 2, 3 or 4,

and to their physiologically acceptable salts.

An object of the invention is to provide novel compounds capable of being used for the preparation of drugs.

Upon further study of the specification and appended claims, further objects and advantages of this invention will become apparent to those skilled in the art.

It has been found that the compounds of the formula I and their physiologically acceptable acid addition salts possess valuable pharmacological properties. Thus, in particular, they are active on the central nervous system, especially in terms of 5-HT_{1A}-agonist and 5-HT-reuptake inhibition. The compounds are furthermore active as serotonin agonists and antagonists. They inhibit the binding of tritiated serotonin ligands to hippocampal receptors (Cossery et al., European J. Pharmacol., 140:143–155 (1987)). They also modify the accumulation of DOPA in the corpus striatum and the accumulation of 5-HTP in the nuclei raphes (Seyfried et al., European J. Pharmacol., 160:31–41 (1989)). They also have analgesic and hypotensive effects; thus, in catheterized, conscious, spontaneously hypertensive rats (strain: SHR/Okamoto/NIH-MO-CHB-Kisslegg; method: q.v. Weeks and Jones, Proc. Soc. Exptl. Biol. Med., 104:646–648 (1960)), the directly measured blood pressure is lowered after oral administration of the compounds. They are also useful for prophylaxis and control of the sequelae of cerebral infarction (apoplexia cerebri) such as stroke and cerebral ischaemia.

Compounds of the formula I and their physiologically acceptable acid addition salts can, therefore, be used as active ingredients for anxiolytics, antidepressants, antipsychotics, neuroleptics, and/or antihypertensives, and also as intermediates for the preparation of other pharmaceutical active ingredients.

The invention relates to the piperidine and piperazine derivatives of the formula I and to their physiologically acceptable acid addition salts.

The radical A is alkyl having 1, 2, 3, 4, 5 or 6 C atoms, especially 1 or 2 C atoms, preferably methyl and also ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or tert-butyl. OA is

preferably methoxy and also ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or tert-butoxy. NHA is preferably methylamino and also ethylamino, isopropylamino, n-butylamino, isobutylamino, sec-butylamino or tert-butylamino. NA_2 is preferably dimethylamino and also N-ethyl-N-methylamino, diethylamino, di-n-propylamino, diisopropylamino or di-n-butylamino.

Analogously, CO—NHA is preferably N-methylcarbamoyl or N-ethylcarbamoyl; CO—NA_2 is preferably N,N-dimethylcarbamoyl or N,N-diethylcarbamoyl.

The radical Ind is an indol-3-yl radical which is unsubstituted or mono- or, for example, disubstituted by the radicals indicated. Preferably, it is substituted in the 5-position. Substitution in the 4-, 6- or 7-position is also suitable. Furthermore, substitution in the 1- or 2-position is possible. Preferred substituents on the indol-3-yl radical are OH, OA, CN, $CONH_2$, CH_2OH, but also CO_2H, F, Cl, Br, I, CH_2NH_2, CONHA or $CONA_2$, where A preferably corresponds to methyl or ethyl.

The radical R^1 is preferably benzofuran-5-yl, 2,3-dihydrobenzofuran-5-yl, chroman-6-yl or chromen-4-on-6-yl, which is unsubstituted or monosubstituted by —CH_2OH, —$CONH_2$, —CO_2A or —CO_2NHA.

Q is preferably —$(CH_2)_4$—, but also —$(CH_2)_2$— or —$(CH_2)_3$—, while Z is preferably —N—, —C (OH)— or —CH—.

Accordingly, the invention relates particularly to those compounds of the formula I in which at least one of said radicals has one of the meanings indicated above, especially one of the preferred meanings indicated above. Some preferred groups of compounds can be expressed by the following partial formulae Ia to Ig, which correspond to formula I and in which the radicals and parameters not described in greater detail are as defined for formula I, but in which:

in Ia, Ind is an indol-3-yl radical substituted in the 5-position by OH or OA;

in Ib, Ind is an indol-3-yl radical substituted in the 5-position by $CONH_2$ or by CN;

in Ic, Z is N and R^1 is substituted or unsubstituted benzofuran-5-yl;

in Id, Z is —C(OH)— and R^1 is substituted or unsubstituted benzofuran-5-yl;

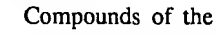
in Ie, Z is N and R^1 is 2,3-dihydrobenzofuran-5-yl;

in If, Z is N and R^1 is chroman-6-yl;

in Ig, Z is N and R^1 is chromen-4-on-6-yl.

Especially preferred compounds are those of partial formulae Ih and Iah to Igh, which correspond to partial formulae I and Ia to Ig, but in which additionally: Q is —$(CH_2)_4$—.

The invention further relates to a process for the preparation of indole derivatives of the formula I and their salts, characterized in that a compound of the formula II



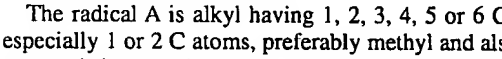
II

wherein

X^1 is X or NH_2,

X is Cl, Br, I, OH or an OH group functionally modified to form a reactive group, and

Ind and Q are as defined, is reacted with a compound of the formula III



III

wherein

X^2 and X^3 can be identical or different and are each X if X^1=NH_2 or are together NH in other cases, and

Z and R^1 are as defined, or in that to prepare a compound of the formula I in which Z is N, a compound of the formula IV

$$Ind—Q—N(CH_2—CH_2—X)_2 \quad IV$$

wherein

X, Q and Ind are as defined, is reacted with a compound of the formula V

$$R^1—NH_2 \quad V$$

wherein

R^1 is as defined, or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more reducible groups and/or one or more additional C—C and/or C—N bonds are treated with a reducing agent,

or in that a compound which has formula I except that one or more hydrogen atoms have been replaced by one or more solvolyzable groups is treated with a solvolyzing agent, and/or in that an OA group is optionally cleaved to form an OH group, and/or an Ind group and/or an Ar group is converted into another Ind and/or Ar group, and/or in that a resulting base or acid of the formula I is converted into one of its salts by treatment with an acid or base.

The compounds of the formula I are otherwise prepared by methods known per se, such as those described in the literature (e.g. in the standard works such as Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York; German Offenlegungsschrift 41 01 686), namely under reaction conditions such as those which are known and suitable for said reactions. It is also possible to make use of variants known per se, which are not mentioned in greater detail here.

If desired, the starting materials for the claimed process can also be formed in situ in such a way that they are not isolated from the reaction mixture but are immediately reacted further to give the compounds of the formula I.

In the compounds of the formula II, X^1 is preferably X; accordingly, in the compounds of the formula III, X^2 and X^3 are together preferably NH. The radical X is preferably Cl or Br, but it can also be I, OH or an OH group functionally modified to form a reactive group, especially alkylsulfonyloxy having 1–6 C atoms (e.g., methanesulfonyloxy) or arylsulfonyloxy having 6–10 C atoms (e.g., benzenesulfonyloxy, p-toluenesulfonyloxy, naphthalene-1- or -2-sulfonyloxy).

Accordingly, the indole derivatives of the formula I can be obtained especially by reacting compounds of the formula Ind—Q—Cl or Ind—Q—Br with piperidine/piperazine derivatives of the formula III in which X^2 and X^3 together are an NH group (designated as IIIa hereafter).

Some of the compounds of the formulae II and, in particular, III are known; the unknown compounds of the formulae II and III can easily be prepared analogously to the known compounds.

Primary alcohols of the formula Ind—Q—OH can be obtained, e.g., by reducing the appropriate carboxylic acids or their esters. Treatment with thionyl chloride, hydrogen bromide, phosphorus tribromide or similar halogen compounds yields the corresponding halides of the formula Ind—Q—Hal. The corresponding sulfonyloxy compounds can be obtained from the alcohols Ind—Q—OH by reaction with the appropriate sulfonyl chlorides.

The iodine compounds of the formula Ind—Q—I can be obtained, e.g., by reacting potassium iodide with the appropriate p-toluenesulfonic acid esters. The amines of the formula Ind—Q—N_2 can be prepared, e.g., from the halides with potassium phthalimide or by reducing the appropriate nitriles.

Most of the piperazine derivatives IIIa are known and can be obtained, e.g., by reacting bis(2-chloroethyl)amine or bis(2-chloroethyl)ammonium chloride with 5-aminobenzofuran, 2,3-dihydro-5-aminobenzofuran, 6-aminochroman or 6-aminochromen-4-one or an appropriately substituted derivative of the compounds mentioned. Compounds of the formula III (X^2 and X^3=X in each case) can be prepared., e.g., by reducing diesters of the formula alky 100C—CH_2—ZR^1—CH_2—COO—alkyl to give compounds of the formula HO—CH_2—CH_2—ZR^1—CH_2-CH_2OH (III, X^2=X^3=OH), this being followed, if desired, by reaction with $SOCl_2$ or PBr_3.

The reaction of the compounds of formulae II and III proceeds according to methods such as those known from the literature for the alkylation of amines. The components can be melted together in the absence of a solvent, in a sealed tube or an autoclave if necessary. It is also possible, however, to react the compounds in the presence of an inert solvent. Examples of suitable solvents are hydrocarbons such as benzene, toluene or xylene; ketones such as acetone or butanone; alcohols such as methanol, ethanol, isopropanol or n-butanol; ethers such as tetrahydrofuran (THF) or dioxane; amides such as dimethylformamide (DMF) or N-methylpyrrolidone; or nitriles such as acetonitrile, or else, if desired, mixtures of these solvents with one another or mixtures with water. It can be favorable to add an acid-binding agent, for example an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or another alkali metal or alkaline earth metal salt of a weak acid, preferably a potassium, sodium or calcium salt, or to add an organic base such as triethylamine, dimethylaniline, pyridine or quinoline, or an excess of the amine component Ind—Q—NH_2 or of the piperidine or piperazine derivative of the formula IIIa. The reaction time is between about a few minutes and 14 days, depending on the conditions used, and the reaction temperature is preferably about 0°–150°, normally 20°–130°.

It is also possible to obtain a compound of the formula I by reacting a compound of the formula Ind—Q—$N(CH_2—CH_2—X)_2$ (IV) with a compound of the formula R^1—NH_2 (V).

Most of the compounds of the formula V are known; the unknown compounds can easily be prepared analogously to the known compounds. For example, starting from the appropriately substituted nitro compounds, they can be converted into the amines of the formula V by reduction. The compounds of the formula IV can be prepared by reaction of Ind—Q—Cl, Ind—Q—Br or Ind—Q—I with secondary amines of the formula $HN(CH_2—CH_2—X)_2$.

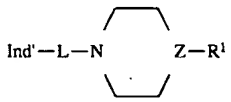
The reaction of compounds IV and V proceeds according to methods which are known from the literature and were given above for the alkylation of amines.

A compound of the formula I can also be obtained by treating a precursor, in which hydrogen atoms have been replaced by one or more reducible groups and/or one or more additional C—C and/or C—N bonds, with a reducing agent, preferably at temperatures of about –80 to 250°, in the presence of at least one inert solvent.

Reducible groups (groups replaceable by hydrogen) are, in particular, oxygen in a carbonyl group, hydroxyl, arylsulfonyloxy (e.g. p-toluenesulfonyloxy), N-benzenesulfonyl, N-benzyl or O-benzyl.

In principle, compounds containing only one of the above-mentioned groups or additional bonds, or compounds containing two or more of the above-mentioned groups or additional bonds adjacent to one another, can be converted into a compound of the formula I by reduction, it being possible simultaneously to reduce substituents in the Ind group which are present in the starting compound. This is preferably carried out using nascent hydrogen or complex metal hydrides or by means of a Wolff-Kishner reduction or the reductions with hydrogen gas under transition metal catalysis.

Preferred starting materials for the reduction have formula VI



VI

wherein

Ind' is an Ind radical which can additionally be substituted in the 1-position by an arylsulfonyl group or an alkyloxycarbonyl group,

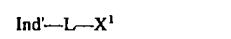
L is Q or a chain which corresponds to the radical Q except that one or more $—CH_2—$ groups have been replaced by —CO— and/or one or more hydrogen atoms have been replaced by one or more OH groups or a double bond, and

R^1 has the meaning given,

but wherein the following meanings cannot apply simultaneously: Ind'=Ind and L=Q.

In the compounds of the formula VI, L is preferably $—CO—(CH_2)_{n-2}—CO—$, wherein n is 2, 3 or 4[specifically —COCO—, $—COCH_2CO—$, $—CO—(CH_2)_2—CO—$, $—CO—(CH_2)_3—CO—$], $—(CH_2)_{n-1}—CO—$, wherein n is 2, 3 or 4 [specifically $—CH_2—CO—$, $—CH_2CH_2—CO—$, $—(CH_2)_3—CO$ —or $—(CH_2)_4—CO—$], further examples being $—CO—CH_2CH_2—$, $—CO—(CH_2)_3—$, $—CH_2—CO—CH_2CH_2—$ or $—CH_2CH_2—CO—CH_2—$.

Compounds of the formula VI can be prepared, e.g., by reacting 4-R^1-piperazine or 4-R^1-piperidine with a compound of the formula VII



VII

wherein

R^1 Ind', L and X^1 are as defined above, under the conditions indicated above for the reaction of II with III.

If nascent hydrogen is used as the reducing agent, this can be produced, e.g., by treating metals with weak acids or with bases. Thus, it is possible, e.g., to use a mixture of zinc with an alkali metal hydroxide solution or a mixture of iron with acetic acid. It is also appropriate to use sodium or another alkali metal dissolved in an alcohol such as ethanol, isopropanol, butanol, amyl or isoamyl alcohol or phenol. It is also possible to use an aluminum-nickel alloy in aqueous-alkaline solution, ethanol being added if necessary. Sodium amalgam or aluminum amalgam in aqueous-alcoholic or aqueous solution is also suitable for producing the nascent hydrogen. The reaction can also be carried out in the heterogeneous phase, in which case it is convenient to use an aqueous phase and a benzene or toluene phase.

Other reducing agents which can be used to particular advantage are complex metal hydrides such as $LiAlH_4$, $NaBH_4$, diisobutylaluminum hydride or $NaAl(OCH_2CH_2OCH_3)_2H_2$, and diborane, catalysts such as BF_3, $AlCl_3$ or LiBr being added if desired. Solvents which are suitable for this purpose are, in particular, ethers such as diethyl ether, di-n-butyl ether, THF, dioxane, diglyme or 1,2-dimethoxyethane, and hydrocarbons such as benzene. Solvents which are suitable for a reduction with $NaBH_4$ are primarily alcohols such as methanol or ethanol, as well as water and aqueous alcohols. Reduction by these methods is preferably carried out at temperatures of about −80 to +150°, especially about 0°–100°.

The reduction of —CO— groups in acid amides (e.g., those of the formula VI in which L is a $—(CH_2)_{n-1}—CO—$ group) to CH_2 groups can be carried out to particular advantage with $LiAlH_4$ in THF at temperatures of preferably about 0°–66°. Arylsulfonyl protecting groups located in the 1-position of the indole ring can be simultaneously eliminated by reduction. N-Benzyl groups can be eliminated by reduction with sodium in liquid ammonia.

It is also possible to reduce one or more carbonyl groups to CH_2 groups according to the Wolff-Kishner method, e.g., by treatment with anhydrous hydrazine in absolute ethanol, under pressure, at temperatures of preferably about 150°–250°. A sodium alcoholate is advantageously used as the catalyst. The reduction can also be varied according to the Huang-Minlon method by carrying out the reaction with hydrazine hydrate in a high-boiling water-miscible solvent such as diethylene glycol or triethylene glycol, in the presence of an alkali such as sodium hydroxide. The reaction mixture is normally boiled for about 3–4 hours. The water is then distilled off and the hydrazone formed is decomposed at temperatures of up to about 200°. The Wolff-Kishner reduction can also be carried out with hydrazine in dimethyl sulfoxide at room temperature.

Moreover, it is possible to carry out certain reductions by using H_2 gas under the catalytic action of transition metals, such as, e.g., Raney Ni or Pd. In this way, e.g., Cl, Br, I, SH or, in certain cases, even OH groups can be replaced by hydrogen. Nitro groups can also be converted into NH_2 groups by catalytic hydrogenation with Pd/H_2 in methanol.

Compounds which have formula I except that one or more H atoms have been replaced by one or more solvolyzable groups can be solvolyzed, especially hydrolyzed, to give the compounds of the formula I.

The starting materials for the solvolysis can be obtained for example by reacting IIIa with compounds which have formula II (X^1=X) except that one or more H atoms have been replaced by one or more solvolyzable groups. Thus, in particular, 1-acylindole derivatives (which have formula I except that, in the 1-position of the Ind radical, they contain an acyl group, preferably an alkoxycarbonyl, alkanoyl, alkylsulfonyl or arylsulfonyl group having up to 10 C atoms in each case, such as methanesulfonyl, benzenesulfonyl or p-toluenesulfonyl) can be hydrolyzed to give the corresponding indole derivatives unsubstituted in the 1-position of the indole ring, e.g. in an acidic or, preferably, neutral or alkaline medium at temperatures of preferably about 0°–200°. Sodium, potassium or calcium hydroxide, sodium or potassium carbonate, or ammonia, is conveniently used as the base. The chosen solvents are preferably water; lower alcohols such as methanol or ethanol; ethers such as THF or dioxane; sulfones such as tetramethylene sulfone; or mixtures thereof, especially mixtures containing water. Hydrolysis can also be carried out simply by treatment with water alone, especially at the boiling point.

A compound of the formula I can furthermore be converted to another compound of the formula I by methods known per se.

Compounds of the formula I in which Ind is an indol- 3-yl radical substituted by CO-R^1 can be obtained by derivatizing

appropriate carboxyindol-3-yl compounds. It is possible, e.g., to esterify the acids with appropriate alcohols or alcoholates, using methods known per se. It is also possible to amidate acids or esters with primary or secondary amines. It is preferred to react the free carboxylic acid with the amine under the conditions of a peptide synthesis. This reaction is preferably carried out in the presence of a dehydrating agent, e.g., a carbodiimide such as dicyclohexylcarbodiimide or else N-(3-dimethylaminopropyl)-N-ethylcarbodiimide, or propanephosphonic anhydride (q.v. Angew. Chem. 92, 129 (1980)), diphenylphosphoryl azide or 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline, in an inert solvent, e.g., a halogenated hydrocarbon such as methylene chloride, an ether such as THF or dioxane, an amide such as DMF or dimethylacetamide, or a nitrile such as acetonitrile, at temperatures of preferably about −10 to 40, preferably about 0°–30°. Instead of the acid or amide, it is also possible to use reactive derivatives of these substances in the reaction, e.g., those in which reactive groups are blocked by protecting groups in an intermediate step. The acids can also be used in the form of their activated esters, which are conveniently formed in situ, e.g., by the addition of 1-hydroxybenztriazole or N-hydroxysuccinimide.

Furthermore, cyano-substituted indol-3-yl radicals can be hydrolyzed to give carboxy-indol-3-yl or carbamido-indol-3-yl radicals.

Conversely, however, it is particularly convenient to prepare the nitriles by elimination of water, starting from the amides, e.g., by means of trichloroacetyl chloride/Et_3N [Synthesis (2), 184, (1985)] or with $POCl_3$ (J. Org. Chem. 26, 1003 (1961)).

A base of the formula I can be converted with an acid into the corresponding acid addition salt. Acids which produce physiologically acceptable salts are suitable for this reaction. Thus, it is possible to use inorganic acids, e.g., sulfuric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, nitric acid and sulfamic acid, as well as organic acids, i.e., specifically aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methanesulfonic or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemonosulfonic and naphthalenedisulfonic acids and laurylsulfuric acid.

If desired, the free bases of the formula I can be liberated from their salts by treatment with strong bases such as sodium or potassium hydroxide or sodium or potassium carbonate provided there are no other acid groups in the molecule. In those cases where the compounds of the formula I have free acid groups, salt formation can also be achieved by treatment with bases. Suitable bases are alkali metal hydroxides, alkaline earth metal hydroxides or organic bases in the form of primary, secondary or tertiary amines.

The invention further relates to the use of the compounds of the formula I and their physiologically acceptable salts for the manufacture of pharmaceutical preparations, especially by a non-chemical route. For this purpose, they can be converted into a suitable dosage form together with at least one excipient or adjunct and, if appropriate, in combination with one or more additional active ingredients.

The invention further relates to compositions, especially pharmaceutical preparations, containing at least one compound of the formula I and/or one of their physiologically acceptable salts. These preparations can be used as drugs in human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral (e.g.,oral), parenteral or topical administration and which do not react with the novel compounds, examples of such excipients being water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. Tablets, coated tablets, capsules, syrups, juices, drops or suppositories are used in particular for enteral administration, solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions or implants are used for parenteral administration, and ointments, creams or powders are used for topical administration. The novel compounds can also be lyophilized and the resulting lyophilizates used, e.g., to manufacture injectable preparations.

The preparations indicated can be sterilized and/or can contain adjuncts such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, colorants, taste correctors and/or flavorings. If desired, they can also contain one or more additional active ingredients, e.g. one or more vitamins.

The compounds of the formula I and their physiologically acceptable salts can be used for the therapeutic treatment of the human or animal body and for controlling diseases. They can be used for treating disorders of the central nervous system, such as tension, depressions and/or psychoses, and side-effects in the treatment of hypertension (e.g., with α-methyldopa). The compounds can also be used in endocrinology and gynecology, e.g., for the therapeutic treatment of acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome and undesired puerperal lactation, and also for the prophylaxis and therapy of cerebral disorders (e.g., migraine), especially in geriatrics in a manner similar to certain ergot alkaloids and for controlling the sequelae of cerebral infarction (apoplexia cerebri), such as stroke and cerebral ischemia.

In these treatments, the substances of the invention are normally administered analogously to known, commercially available preparations (e.g., bromocriptine, dihydroergocornine), preferably in dosages of about 0.2–500 mg, especially 0.2–50 mg per dosage unit. The daily dosage is preferably about 0.001–10 mg/kg of body weight. The low dosages (about 0.2–1 mg per dosage unit; about 0.001–0.005 mg/kg of body weight) are particularly suitable for use as antimigraine preparations; dosages of about 10–50 mg per dosage unit are preferred for the other indications. However, the particular dose for each individual patient depends on a very wide variety of factors, for example, the activity of the particular compound used, age, body weight, general state of health, sex, diet, time and method of administration, rate of excretion, drug combination and severity of the particular disease to which the therapy is applied. Oral administration is preferred.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight.

The entire disclosure of all applications, patents and publications, cited above and below, and of corresponding

German application P 43 33 254.4, filed Sep. 30, 1993, are hereby incorporated by reference.

In the following Examples, "working-up in conventional manner" means: Water is added if necessary, extraction is carried out with methylene chloride, the organic phase is separated off, dried over sodium sulfate and filtered, the filtrate is evaporated and the residue is purified by chromatography on silica gel and/or by crystallization. Temperatures are given in ° C. Rf values were obtained by thin layer chromatography on silica gel.

EXAMPLES

Example 1

1.8 g of 3-(4-chlorobutyl)-5-methoxyindole [obtainable by diazotization of p-methoxyaniline, reaction with ethyl cyclohexanone-2-carboxylate according to Japp-Klingemann to give 4-(2-carbethoxyindol-3-yl)butyric acid, alkaline hydrolysis, decarboxylation, reduction with $LiAlH_4$ and reaction with $SOCl_2$] and 1.9 g of 1-(2-hydroxymethylbenzofuran-5-yl)piperazine [obtainable by reaction of N,N-bis(2-chloroethyl)amine with 2-hydroxymethyl-5-aminobenzofuran] are dissolved in 200 ml of acetonitrile and the mixture is stirred at room temperature for 10 hours. Customary working up gives 1-[4-(5-methoxyindol-3-yl)butyl] -4-(2-hydroxymethylbenzofuran- 5-yl)piperazine, m.p. 159°.

The following are obtained analogously by reaction of 3-(4-chlorobutyl)-5-methoxyindole with 1-(2,3-dihydrobenzofuran- 5-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine, m.p. 111°–112°;

of 3-(4-chlorobutyl)-5-hydroxyindole with 1-(chroman-6-yl)piperazine:

1-[4-(5-hydroxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine, m.p. 220°–222°;

of 3-(4-chlorobutyl)-5-methoxyindole with 1-(chroman-6-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine, m.p. 129°–130°;

of methyl 3-(4-chlorobutyl)-5-indolecarboxylate with 1-(chroman-6-yl)piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of ethyl 3-(4-chlorobutyl)-5-indolecarboxylate with 1-(benzofuran-5-yl)piperazine:

1-[4-(5-ethoxycarbonylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxyindole with 1-(benzofuran-5-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 1-(chromen-4-on-6-yl)piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine;

of 3-(4-chlorobutyl)-5-cyanoindole with 1-(chromen-4-on-6-yl)piperazine:

1-[4-(5-cyanoindol-3-yl)butyl]-4-(chromen-4-on 6-yl)piperazine;

of 3-(4-chlorobutyl)-5-chloroindole with 1-(2,3-dihydrobenzofuran- 5-yl)piperazine:

1-[4-(5-chloroindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 1-(2,3-dihydrobenzofuran-5-yl)piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 4-(2,3-dihydrobenzofuran-5-yl)piperidine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperidine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 4-(2,3-dihydrobenzofuran-5-yl)-4-hydroxypiperidine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)-4-hydroxypiperidine;

of 3-(4-chlorobutyl)-5,6-dimethoxyindole with 1-(chroman-6-yl)piperazine:

1-[4-(5,6-dimethoxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of 3-(4-chlorobutyl)-5-cyanoindole with 1-(2-carboxybenzofuran- 5-yl)piperazine:

1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-6-fluoroindole with 1-(2,3-dihydrobenzofuran- 5-yl)piperazine:

1-[4-(6-fluoroindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine.

Example 2

1.8 g of 1-[4-(5-methoxycarbonylindol-3-yl)-butyl]-4-(chroman-6-yl)piperazine [obtainable according to Example 1] are boiled for 0.5 hours with 100 ml of 2N ethanolic KOH, worked up in the customary manner and give 1-[4-(5-carboxyindol-3-yl)butyl]-4-(chreman-6-yl)piperazine.

The following are obtained analogously by alkaline hydrolysis of the corresponding esters starting from 1-[4-(5-ethoxycarbonylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine:

1-[4-(5-carboxyindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine:

from 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine:

1-[4-(5-carboxyindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine;

from 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine:

1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine;

from 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)-4-hydroxypiperidine;

1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)-4-hydroxypiperidine.

Example 3

2.8 g of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine are suspended in 100 ml of N-methylpyrrolidine. 3.2 g of 2-chloro-1-methylpyridinium methanesulfonate are then added and the mixture is stirred at room temperature for 12 hours. Dried NH_3 gas is then passed into the resulting solution until it is saturated and the mixture is stirred again for 10 hours. Customary working up gives 1-[4-(5-carbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)-piperazine.

The following are obtained analogously by amidation of the following carboxylic acids with 2-chloro-1-methylpyridinium methanesulfonate:

from 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobinzofuran- 5-yl)piperidine

1-[4-(5-carbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperidine, m.p. 155–157°;

from 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)-4-hydroxypiperidine

1-[4-(5-carbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)-4-hydroxypiperidine, m.p. 69° (dec.);

from 1-[4-(5-carboxyindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine

1-[4-(5-carbamoylindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine.

Example 4

Analogously to Example 3, starting from 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine reaction with 2-chloro-l-methylpyridinium methanesulfonate gives 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoylbenzofuran-5-yl)piperazine, m.p. 269–272° (hydrochloride).

Example 5

A mixture of 2.6 g of 3-(2-aminoethyl)-5-cyanoindole [obtainable by reaction of 5-cyanoindole with 2-chloroacetyl chloride to give 3-(2-chloroacetyl)-5-cyanoindole, subsequent reduction with diborane, reaction with phthalimide and hydrolysis]and one equivalent of 5-[N,N-bis(2-chloroethyl)amino]benzofuran [obtainable by reaction of 2-chloroacetyl chloride with 5-aminobenzofuran and subsequent reduction with diborane] in 40 ml of acetone and 40 ml of water is boiled for 20 hours and then worked up in the customary manner. 1-[2-(5-Cyanoindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine is obtained.

The following are obtained analogously by reaction of 5-[N,N-bis(2-chloroethyl)amino]benzofuran with 3-(4-aminobutyl)-5-methoxymethylindole:

1-[4-(5-methoxymethylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine; with 3-(3-aminopropyl) -5-hydroxyindole:

1-[3-(5-hydroxyindol-3-yl)propyl]-4-(benzofuran-5-yl)piperazine;

with 3-(2-aminoethyl)-5-methoxyindole:

1-[2-(5-methoxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine;

with methyl 3-(3-aminopropyl)-5-indolecarboxylate:

1-[3-(5-methoxycarbonylindol-3-yl)propyl]-4-(benzofuran- 5-yl)piperazine;

with ethyl 3-(2-aminoethyl)-5-indolecarboxylate:

1-[2-(5-ethoxycarbonylindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine;

with 3-(4-aminobutyl)-5-fluoroindole:

1-[4-(5-fluoroindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

with 3-(3-aminopropyl)-5-cyanoindole:

1-[3-(5-cyanoindol-3-yl)propyl]-4-(benzofuran- 5-yl)piperazine.

Example 6

Analogously to Example 5, reaction of 3.2 g of 3-(2-aminoethyl)-5-methoxyindole with 1.3 equivalents of 6-[N, N-bis(2-chloroethyl)amino]chroman [obtainable by reaction of 2-chloroacetyl chloride with 6-aminochroman and subsequent reduction with diborane] gives 1-[2-(5-methoxyindol-3-yl)ethyl]-4-(chroman-6-yl)piperazine.

The following are obtained analogously by reaction of 6-[N,N-bis(2-chloroethyl)amino]chroman with 3-(4-aminobutyl)-5-methoxymethylindole:

1-[4-(5-methoxymethylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

with 3-(3-aminopropyl)-5-hydroxyindole:

1-[3-(5-hydroxyindol-3-yl)propyl]-4-(chroman-6-yl)-piperazine;

with 3-(2-aminoethyl)-5-methoxyindole:

1-[2-(5-methoxyindol-3-yl)ethyl]-4-(chroman-6-yl)piperazine;

with methyl 3-(3-aminopropyl)-5-indolecarboxylate:

1-[3-(5-methoxycarbonylindol-3-yl)propyl]-4-(chroman-6-yl)piperazine;

with ethyl 3-(2-aminoethyl)-5-indolecarboxylate:

1-[2-(5-ethoxycarbonylindol-3-yl)ethyl]-4-(chroman-6-yl)piperazine;

with 3-(4-aminobutyl)-5-fluoroindole:

1-[4-(5-fluoroindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine;

with 3-(3-aminopropyl) -5-cyanoindole:

1-[3-(5-cyanoindol-3-yl) propyl]-4-(chroman-6-yl)piperazine.

Example 7

A solution of 3.9 g of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine in 250 ml of DMF is treated with 1 g of N-methylmorpholine. A solution of one equivalent of tert-butylamine in 5 ml of DMF, 1.3 g of 1-hydroxybenzotriazole and a solution of 1.9 g of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in 20 ml of DMF are added with stirring. The mixture is stirred at room temperature for 16 hours and the filtrate is evaporated. Customary working up gives 1-[4-(5-N-tert-butylcarbamoylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran-5-yl)piperazine.

The following are obtained analogously by reaction with tert-butylamine starting

from 1-[4-(5-carboxyindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine:

1-[4-(5-N-tert-butylcarbamoylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine:

from 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran- 5-yl)piperazine:

1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-N-tert-butyl-carbamoylbenzofuran- 5-yl)piperazine.

Example 8

A mixture of 2.1 g of 1-[4-(5-methoxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine [can be prepared according to Example 1], 1.8 g of pyridine hydrochloride and 50 ml of pyridine is boiled for 3 hours. It is cooled and evaporated, and the residue is worked up in the customary manner and gives 1-[4-(5-hydroxyindol-3-yl)-butyl]-4-(chroman-6-yl)piperazine, m.p. 220°–222°.

The following are obtained analogously

from 1-[4-(5-methoxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine:

1-[4-(5-hydroxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine;

from 1-[4-(5-methoxyindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine:

1-[4-(5-hydroxyindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

from 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine:

1-[4-(5-hydroxycarbonylindol-3-yl) butyl]-4-(chromen-4-on-6-yl) piperazine;

from 1-[4-(5-methoxymethylindol-3-yl)butyl]-4-(benzofuran- 5-yl)piperazine:

1-[4-(5-hydroxymethylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

from 1-[2-(5-methoxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine:

1-[2-(5-hydroxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine;

from 1-[2-(5-methoxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine:

1-[2-(5-hydroxyindol-3-yl)ethyl]-4-(benzofuran-5-yl)piperazine.

Example 9

Analogously to Example 1, starting from 3-(4-chlorobutyl)-5-cyanoindole [obtainable by reaction of 5-cyanoindole with 4-chlorobutyryl chloride to give 3-(4-chlorobutyryl)-5-methoxyindole and subsequent reduction with $NaAlH_2(OCH_2CH_2OCH_3)_2$] by reaction with 1-(2-ethoxy-carbonylbenzofuran-5-yl)piperazine [obtainable by reaction of N,N-bis(2-chloroethyl)amine with 2-ethoxy-carbonyl-5-aminobenzofuran] gives, after customary working up, 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-ethoxy-carbonylbenzofuran- 5-yl)piperazine, m.p. 221°–223° (dihydrochloride).

The following are obtained analogously by reaction of 3-(4-chlorobutyl)-5-methoxyindole with 1-(2-cyano-benzofuran- 5-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(2-cyanobenzofuran-5-yl)piperazine;

of 3-(4-chlorobutyl)-5,6-dimethoxyindole with 1-(chroman-6-yl) piperazine:

1-[4-(5,6-dimethoxyindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of 3-(4-chlorobutyl)-5,6-difluoroindole with 1-(chroman-6-yl)piperazine:

1-[4-(5,6-difluoroindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of methyl 3-(4-chlorobutyl)-6-indolecarboxylate with 1-(chroman-6-yl)piperazine:

1-[4-(6-methoycarbonylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of ethyl 3-(3-chloropropyl)-6-indolecarboxylate with 1-(2-cyanobenzofuran-5-yl)piperazine:

1-[3-(6-ethoxycarbonylindol-3-yl)propyl]-4-(2-cyanobenzofuran- 5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxyindole with 1-(2-N-methylcarbamoylbenzofuran- 5-yl)piperazine:

1-[4-(5-methoxyindol-3-yl)butyl]-4-(2-N-methylcarbamoylbenzofuran- 5-yl)piperazine;

of 3-(4-chlorobutyl)-6-chloroindole with 1-(chromen-4-on-6-yl)piperazine:

1-[4-(6-chloroindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine;

of 3-(2-chloroethyl)-5-cyanoindole with 1-(chromen-4-on-6-yl)piperazine:

1-[2-(5-cyanoindol-3-yl)ethyl]-4-(chromen-4-on-6-yl)piperazine;

of 3-(2-chloroethyl)-5,6-dichloroindole with 1-(2,3-dihydrobenzofuran- 5-yl)piperazine:

1-[2-(5,6-dichloroindol-3-yl)ethyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine;

of 3-(4-chlorobutyl)-5-methoxycarbonylindole with 1-(2-carboxybenzofuran-5-yl)piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2-carboxybenzofuran- 5-yl)piperazine;

of 3-(2-chloroethyl)-5-methoxycarbonylindole with 4-(2-carboxybenzofuran-5-yl)piperidine:

1-[2-(5-methoxycarbonylindol-3-yl)ethyl]-4-(2-carboxybenzofuran- 5-yl)piperazine;

of 3-(4-chlorobutyl)-6-methoxycarbonylindole with 4-(3-carboxybenzofuran-5-yl)-4-hydroxypiperidine:

1-(4-(6-methoxycarbonylindol-3-yl)butyl]-4-(3-carboxybenzofuran- 5-yl)-4-hydroxypiperidine;

of 3-(4-chlorobutyl)-7-methoxycarbonylindole with 4-(3-carboxybenzofuran-5-yl)-4-hydroxypiperidine;

1-[4-(7-methoxycarbonylindol-3-yl)butyl]-4-(3-carboxybenzofuran- 5-yl)-4-hydroxypiperidine;

of 3-(4-chlorobutyl)-5,6-dimethoxyindole with 1-(2-carboxybenzofuran- 5-yl)piperazine:

1-[4-(5,6-dimethoxyindol-3-yl)butyl]-4-(2-carboxybenzofuran- 5-yl)piperazine.

Example 10

A solution of 3.6 g of 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chromen-4-on-6-yl)piperazine in 40 ml of THF is added dropwise with stirring at room temperature to a suspension of 0.6 g of lithium aluminum hyride in 20 ml of THF. The mixture is then stirred for a further hour at 25° C., 20 ml of dilute sodium hydroxide solution are added, the mixture is filtered and the filtrate is worked up in the customary manner. 1-[4-(5-Hydroxymethylindol-3-yl)butyl] -4-(chromen-4-on-6-yl)piperazine is obtained.

The following are obtained analagously by reduction of 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine

1-[4-(5-hydroxymethylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-benzofuran-5yl)piperazine

1-[4-(5-hydroxymethylindol-3-yl)butyl]-4-(benzofuran-5-yl)piperazine;

of 1-[3-(5-methoxycarbonylindol-3-yl)propyl]-4-(chroman-6-yl) piperidine

1-[3-(5-hydroxymethylindol-3-yl)propyl]-4-(chroman-6-yl)piperidine

of 1-[2-(5-methoxycarbonylindol-3-yl)ethyl]-4-chroman-6-yl) piperidine

1-[2-(5-hydroxymethylindol-3-yl)ethyl]-4-(chroman-6-yl)piperidine.

Example 11

HCl gas is passed into a boiling solution of 2.5 g of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine in 50 ml of absolute methanol for 2 hours. The mixture is then boiled for a further hour, worked up in the customary manner and gives 1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)piperazine.

The following are obtained analagously by esterification of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)-4-hydroxypiperidine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(2,3-dihydrobenzofuran- 5-yl)-4-hydroxypiperidine;

of 1-[4-(5-carboxyindol-3-yl)butyl]-4-(chroman-6-yl)-piperazine:

1-[4-(5-methoxycarbonylindol-3-yl)butyl]-4-(chroman-6-yl)piperazine;

of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carboxybenzofuran-5-yl)piperazine:

1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-methoxycarbonylbenzofuran- 5-yl)piperazine.

Example A

Injection vials

A solution of 100 g of an active ingredient of the formula I and 5 g of disodium hydrogen phosphate in 3 l of double-distilled water is adjusted to pH 6.5 with 2N hydrochloric acid, sterile-filtered, filled into injection vials, lyophilized and sterile-sealed. Each injection vial contains 5 mg of active ingredient.

Example B

Suppositories

A mixture of 20 mg of an active ingredient of the formula I is melted with 100 g of soya lecithin and 1,400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active ingredient.

Example C

Solution

A solution of 1 g of an active ingredient of the formula I, 9.38 g of $NaH_2PO_4 \times 2H_2O$, 28.48 g $Na_2HPO_4 \times 12\ H_2O$ and 0.1 g of benzalkonium chloride is prepared in 940 ml of double-distilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilized by irradiation. This solution can be used in the form of eyedrops.

Example D

Ointment

500 mg of an active ingredient of the formula I are mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example E

Tablets

A mixture of 1 kg of active ingredient of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed to tablets in conventional manner so that each tablet contains 10 mg of active ingredient.

Example F

Coated tablets

Tablets are formed by compression analogously to Example E and then covered in conventional manner with a coating of sucrose, potato starch, talc, tragacanth and colorant.

Example G

Capsules

2 kg of active ingredient of the formula I are filled into hard gelatin capsules in conventional manner so that each capsule contains 20 mg of the active ingredient.

Example H

Ampoules

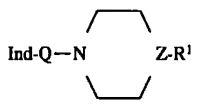
A solution of 1 kg of active ingredient of the formula I in 60 l of double-distilled water is filled into ampoules and lyophilized under aseptic conditions and the ampoules are sealed under sterile conditions. Each ampoule contains 10 mg of active ingredient.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A compound according to formula I



I

wherein

Ind is unsubstituted indol-3-yl, indol-3-yl monosubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2, or indol-3-yl polysubstituted by OH, OA, CN, Hal, COR^2, CH_2R^2 or combinations thereof;

R^1 is benzofuran-5-yl, chroman-4-on-6-yl, 3-chromen-6-yl or chromen-4-on-6-yl, which in each case is unsubstituted or monosubstituted by CN, CH_2OH, CH_2OA or COR^2;

Q is C_mH_{2m};

Z is N;

A is alkyl having 1–6 C atoms;

Hal is F, Cl, Br or I;

R^2 is OH, OA, NH_2, NHA or NA_2;

$R^3$is H, OH or OA; and

m is 2, 3 or 4; or

a physiologically acceptable salt thereof.

2. A compound according to claim **1**, wherein said compound is:

(a) 1-[4-(5-methoxyindol-3-yl)butyl]-4-(2-hydroxymethylbenzofuran- 5-yl)piperazine or a physiologically acceptable salt thereof;

(b) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-ethoxycarbonylbenzofuran- 5-yl) piperazine or a physiologically acceptable salt thereof; or

(c) 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoylbenzofuran- 5-yl) piperazine or a physiologically acceptable salt thereof.

3. A compound according to claim **1**, wherein Ind is unsubstituted indol-3-yl, indol-3-yl monosubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2, or indol-3-yl disubstituted by OH, OA, CN, Hal, COR^2 or CH_2R^2.

4. A compound according to claim **1**, wherein Ind is indol-3-yl monosubstituted in the 5-position by OH, OA, CN, Hal, COR^2 or CH_2R^2.

5. A compound according to claim 1, wherein Ind is indol-3-yl monosubstituted in the 4-, 6- or 7-position by OH, OA, CN, Hal, COR^2 or CH_2R^2.

6. A compound according to claim 1, wherein A is methyl or ethyl.

7. A compound according to claim 1, wherein R^1 is benzofuran-5-yl, or chroman-4-on-6-yl which, in each case is unsubstituted or monosubstituted by $—CH_2OH$, $—CONH_2$, $—CO_2A$ or $—CO_2NHA$.

8. A compound according to claim 1, wherein Q is $—(CH_2)_4—$.

9. A compound according to claim 1, wherein Ind is indol-3-yl substituted in the 5-position by OH or OA.

10. A compound according to claim 1, wherein Ind is indol-3-yl substituted in the 5-position by $CONH_2$ or CN.

11. A compound according to claim 1, wherein R^1 is unsubstituted benzofuran-5-yl or benzofuran-5-yl substituted by CN, CH_2OH, CH_2OA or COR^2.

12. A compound according to claim 1, wherein R^1 is chromen-4-on-6-yl.

13. A compound according to claim 1, wherein R^1 is unsubstituted 3-chromen-6-yl or 3-chromen-6-yl substituted by CN, CH_2OH, CH_2OA or COR^2.

14. A compound according to claim 1, wherein R^1 is unsubstituted chroman-4-on-6-yl or chroman-4-on-6-yl substituted by CN, CH_2OH, CH_2OA or COR^2.

15. A compound according to claim 1, wherein R^1 is unsubstituted chromen-4-on-6-yl or chromen-4-on-6-yl substituted by CN, CH_2OH, CH_2OA or COR^2.

16. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

17. A composition according to claim 16, wherein said compound is present in an amount of 0.2–500 mg.

* * * * *

EXHIBIT 2

Executed Assignment

MERCK 1617

ASSIGNMENT

WHEREAS the below named inventor (if only one inventor is named below) or inventors (if plural inventors are named below) hereinafter referred to as the ASSIGNOR invented a certain improvement relating to

PIPERIDINES AND PIPERAZINES

☒ for which an application for Letters Patent to be filed in the United States Patent and Trademark Office was executed on even date.

☒ for which U.S. Application Serial No. 08/314,734 for Letters Patent was filed in the U.S. Patent and Trademark Office on _____

☐ for which an International Application was filed on _____ PCT/ / designating the United States

AND WHEREAS

MERCK PATENT GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG,
D-64271 Darmstadt, Fed. Rep. of Germany

hereinafter referred to as the ASSIGNEE, is desirous of acquiring the entire right, title, and interest in and to said invention and application, including any and all divisions and continuations thereof, and any and all Letters Patent which may be granted thereon, including any and all renewals, reissues, and prolongations thereof.

NOW, THIS WITNESSETH that for good and valuable consideration, the receipt whereof is hereby acknowledged, ASSIGNOR hereby assigns, sells, and transfers to ASSIGNEE, its assigns and legal representatives, the entire and exclusive right, title, and interest in and to said invention and application, including any and all divisions and continuations thereof, and any and all Letters Patent which may be granted therefor, including any and all renewals, reissues, and prolongations thereof, ASSIGNEE, its assigns and legal representatives to have, hold, exercise, and enjoy said invention and application, including any and all divisions and continuations thereof, and any and all Letters Patent which may be granted therefor, including any and all renewals, reissues, and prolongations thereof, with all the rights, powers, privileges and advantages in anywise arising from or appertaining thereto, for and during the term or terms of any and all such Letters Patent when granted, including any and all renewals, reissues, prolongations thereof, for the use and benefit of ASSIGNEE and its assigns and legal representatives, in as ample and beneficial a manner to all intents and purposes as the ASSIGNOR might or could have held and enjoyed the same, if the assignment had not been made.

AND ASSIGNOR hereby agrees to execute all papers that may be necessary to file applications in the United States for said invention and to assign the same to said ASSIGNEE, its assigns and legal representatives and to execute any other papers that may be needed in connection with filing said application and securing a Letters Patent thereon.

AND ASSIGNOR authorizes and requests the Commissioner of Patents and Trademarks to issue a Letters Patent on said application, and on any and all divisions and continuations thereof, to ASSIGNEE, its assigns and legal representatives, in accordance herewith.

The undersigned hereby grant(s) the law firm of Millen, White, Zelano & Branigan, P.C. the power to insert on this assignment any further identification which may be necessary or desirable in order to comply with the rules of the United States Patent and Trademark Office for recordation of this document.

IN TESTIMONY WHEREOF this assignment is executed by ASSIGNOR.

201	FULL NAME OF SOLE OR FIRST NAMED INVENTOR Henning BÖTTCHER	INVENTOR'S SIGNATURE	DATE September 20, 1994
202	FULL NAME OF SECOND JOINT INVENTOR, IF ANY Christoph SEYFRIED	INVENTOR'S SIGNATURE	DATE September 20, 1994
203	FULL NAME OF THIRD JOINT INVENTOR, IF ANY Gerd BARTOSZYK	INVENTOR'S SIGNATURE	DATE September 20, 1994
204	FULL NAME OF FOURTH JOINT INVENTOR, IF ANY Hartmut GREINER	INVENTOR'S SIGNATURE	DATE September 20, 1994
205	FULL NAME OF FIFTH JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
206	FULL NAME OF SIXTH JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
207	FULL NAME OF SEVENTH JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
208	FULL NAME OF EIGHTH JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
209	FULL NAME OF NINTH JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
210	FULL NAME OF TENTH JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
211	FULL NAME OF ELEVENTH JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE
212	FULL NAME OF TWELFTH JOINT INVENTOR, IF ANY	INVENTOR'S SIGNATURE	DATE

MWZ 16a

EXHIBIT 3

Letter on Behalf of the Marketing Applicant Authorizing the Patent Owner to Rely upon the Activities of the Marketing Applicant

TROVIS PHARMACEUTICALS
Uncovering the possibilities.

One Gateway Center, Suite 702
Newton, MA 02458

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FAX 617 965 0445

WWW.TROVISPHARMA.COM

March 14, 2011

VIA HAND DELIVERY

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
For Patent Examination Policy
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Re: *Patent Term Extension for U.S. Patent No. 5,532,241*

Dear Ms. Till:

On behalf of Trovis Pharmaceuticals LLC, Marketing Applicant for New Drug Application No. 22-567 for VIIBRYD™ (vilazodone hydrochloride), its predecessors and affiliates, I hereby authorize the patent owner of record, Merck Patent GmbH, in connection with its application for extension of U.S. Patent No. 5,532,241 to rely upon the activities of Trovis Pharmaceuticals LLC, its predecessors and affiliates, undertaken in connection with seeking approval by the Food and Drug Administration of NDA No. 22-567. Trovis Pharmaceuticals LLC is a licensee of Merck KGaA, of which Merck Patent GmbH is the trustee with respect to patent matters, under this patent.

Respectfully Submitted,

Caesar J. Belbel
EVP & Chief Legal Officer

EXHIBIT 4

Power of Attorney

MERCK

Merck Patent GmbH · Germany · Frankfurter Str. 250 · 64293 Darmstadt

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
For Patent Examination Policy
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
USA

Date	March 16, 2011
Division/Dept.	Patents Pharmaceuticals
Care of	Dr. Bauer
Phone	+ 49 6151 72-21 04
Fax	+ 49 6151 72-71 91
E-Mail	patent@merck.de
Your letter	
Your ref.	

VIA HAND DELIVERY

Re: Patent Term Extension for U.S. Patent No. 5,532,241

Dear Ms. Till:

This is to advise you that, as authorized representatives of Merck Patent GmbH ("Merck"), owner of U.S. Patent No. 5,532,241 ("the '241 patent"), we hereby authorize Trovis Pharmaceuticals LLC, a subsidiary of Clinical Data, Inc., of One Gateway Center, Suite 702, Newton, MA ("Trovis") to file and prosecute the patent term extension application pursuant to 35 U.S.C. §156 for the '241 patent ("the Application") on behalf of Merck, pursuant to 37 CFR §1.730(c). We understand that counsel for McCarter & English, 265 Franklin Street, Boston, MA, and Scott A.M. Chambers, counsel for Patton Boggs LLP, 8484 Westpark Drive, 9th Floor, McLean, Virginia 22102 will file and prosecute the Application as Trovis' representative, pursuant to 37 CFR §1.730(c), and hereby grant McCarter & English and Patton Boggs LLP any authorizations from Merck necessary for McCarter and English and Patton Boggs LLP to act in this capacity.

Respectfully Submitted,

Merck Patent GmbH

i.V.
Dr. Bauer

i.V.
Dr. Wodopia

Merck Patent GmbH
Postfach · 64271 Darmstadt
Frankfurter Straße 250 · 64293 Darmstadt
Telefon 06151/72-0
Telefax 06151/72-7191

Bankkonto:
103648 Deutsche Bank AG,
Filiale Darmstadt (BLZ 508 700 05)

Geschäftsführer:
Dr. Wolfgang Losert
Sitz der Gesellschaft: Darmstadt

EXHIBIT 5

Approved Label

VIIBRYD™ (vilazodone hydrochloride) Tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VIIBRYD™ safely and effectively. See full prescribing information for VIIBRYD.

VIIBRYD (vilazodone HCl) Tablets for oral administration
Initial U.S. Approval: 2011

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

See full prescribing information for complete boxed warning.
Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders (5.1).
VIIBRYD is not approved for use in pediatric patients (8.4).

INDICATIONS AND USAGE

VIIBRYD is indicated for the treatment of major depressive disorder (MDD). The efficacy of VIIBRYD was established in two 8-week, placebo-controlled trials in adult patients with MDD (1, 14).

DOSAGE AND ADMINISTRATION

- The recommended dose for VIIBRYD is 40 mg once daily (2).
- VIIBRYD should be titrated to the 40 mg dose, starting with an initial dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then increased to 40 mg once daily (2).
- VIIBRYD should be taken with food. Administration without food can result in inadequate drug concentrations and may diminish effectiveness (2, 12.3).
- When discontinuing treatment, reduce the dose gradually (2.4).

DOSAGE FORMS AND STRENGTHS

VIIBRYD is available as 10 mg, 20 mg and 40 mg tablets (3).

CONTRAINDICATIONS

- **Monoamine Oxidase Inhibitors**: Do not use VIIBRYD concomitantly with an MAOI or within 14 days of stopping or starting an MAOI (4.1).

WARNINGS AND PRECAUTIONS

Clinical Worsening/Suicide Risk: Monitor patients for clinical worsening and suicidal thinking or behavior (5.1).
Serotonin Syndrome or Neuroleptic Malignant (NMS)-like Syndrome: Can occur with treatment. Discontinue and initiate supportive treatment (5.2).
Seizures: Can occur with treatment. Use with caution in patients with a seizure disorder (5.3).
Abnormal Bleeding: Treatment can increase the risk of bleeding. Use with caution in association with nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or other drugs that affect coagulation (5.4).
Activation of Mania/Hypomania: Can occur with treatment. Screen patients for bipolar disorder (5.5).
Discontinuation of Treatment with VIIBRYD: A gradual reduction in dose is recommended rather than an abrupt cessation (5.6).
Hyponatremia: Can occur in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (5.7).

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) are: diarrhea, nausea, vomiting, and insomnia (6).
To report SUSPECTED ADVERSE REACTIONS, contact Trovis Pharmaceuticals at 1-877-878-7200 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

MAOIs: Do not use VIIBRYD concomitantly with an MAOI or within 14 days of stopping or starting an MAOI (4.1, 7.1).
CYP3A4 inhibitors: The VIIBRYD dose should be reduced to 20 mg when co-administered with CYP3A4 strong inhibitors (7.3).
CYP3A4 inducers: Concomitant use of VIIBRYD with inducers of CYP3A4 can result in inadequate drug concentrations and may diminish effectiveness. The effect of CYP3A4 inducers on systemic exposure of vilazodone has not been evaluated (7.3).

USE IN SPECIFIC POPULATIONS

Pregnancy: There are no controlled human data regarding VIIBRYD use during pregnancy. Use only if the potential benefits outweigh the potential risks (2.3, 8.1).
Nursing Mothers: There are no human data regarding VIIBRYD concentrations in breast milk. Women should breast feed only if the potential benefits outweigh the potential risks (8.3, 2.3).
Pediatric Use: The safety and efficacy of VIIBRYD in pediatric patients have not been studied (8.4).
Geriatric Use: No dose adjustment is recommended on the basis of age (8.5).
Hepatic Impairment: No dose adjustment is recommended in patients with mild or moderate hepatic impairment. VIIBRYD has not been studied in patients with severe hepatic impairment (8.6).
Renal Impairment: No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment. (8.7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: January 2010

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed**

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of VIIBRYD or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. VIIBRYD is not approved for use in pediatric patients [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4), and Patient Counseling Information (17.1)*]

1 INDICATIONS AND USAGE

VIIBRYD is indicated for the treatment of major depressive disorder (MDD). The efficacy of VIIBRYD was established in two 8-week, randomized, double-blind, placebo-controlled trials in adult patients with a diagnosis of MDD *[see Clinical Studies (14)]*.

Major depressive disorder consists of one or more major depressive episodes. A major depressive episode (DSM-IV-TR) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Treatment of Major Depressive Disorder

The recommended dose for VIIBRYD is 40 mg once daily. VIIBRYD should be titrated, starting with an initial dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then an increase to 40 mg once daily. VIIBRYD should be taken with food. VIIBRYD blood concentrations (AUC) in the fasted state can be decreased by approximately 50% compared to the fed state, and may result in diminished effectiveness in some patients *[see Pharmacokinetics (12.3)]*.

2.2 Maintenance/Continuation/Extended Treatment

The efficacy of VIIBRYD has not been systematically studied beyond 8 weeks. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Patients should be reassessed periodically to determine the need for maintenance treatment and the appropriate dose for treatment.

2.3 Dosing in Special Populations

Pregnant Women: Neonates exposed to serotonergic antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. When treating pregnant women with VIIBRYD, consider whether the potential benefits outweigh the potential risks of treatment *[see Pregnancy (8.1)]*.

Nursing Mothers: There are no clinical data regarding the effect of VIIBRYD on lactation and nursing *[see Nursing Mothers (8.3)]*. Breastfeeding in women treated with VIIBRYD should be considered only if the potential benefit outweighs the potential risk.

Pediatric Patients: The safety and efficacy of VIIBRYD have not been studied in pediatric patients *[see Pediatric Use (8.4)]*.

Geriatric Patients: No dose adjustment is recommended on the basis of age *[see Geriatric Use (8.5)]*.

Hepatic Impairment: No dose adjustment is recommended in patients with mild or moderate hepatic impairment. VIIBRYD has not been studied in severe hepatic impairment *[see Hepatic Impairment (8.6)]*.

Renal Impairment: No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment. *[see Renal Impairment (8.7)]*.

Gender: No dose adjustment is recommended on the basis of gender *[see Gender Effect (8.8)]*.

2.4 Discontinuing Treatment

Discontinuation symptoms have been reported with discontinuation of serotonergic drugs such as VIIBRYD. Gradual dose reduction is recommended, instead of abrupt discontinuation, whenever possible. Monitor patients for these symptoms when discontinuing VIIBRYD. If intolerable symptoms occur following a dose decrease or upon discontinuation of treatment, consider resuming the previously prescribed dose and decreasing the dose at a more gradual rate *[see Warnings and Precautions (5.6)]*.

2.5 Monoamine Oxidase Inhibitors (MAOI)

At least 14 days must elapse between discontinuation of an MAOI and initiation of therapy with VIIBRYD. In addition, at least 14 days must be allowed after stopping VIIBRYD before starting an MAOI *[see Contraindications (4.1)]*.

3 DOSAGE FORMS AND STRENGTHS

VIIBRYD Tablets are available as 10 mg, 20 mg and 40 mg immediate-release, film-coated tablets.
10 mg pink, oval tablet, debossed with 10 on one side
20 mg orange, oval tablet, debossed with 20 on one side
40 mg blue, oval tablet, debossed with 40 on one side

4 CONTRAINDICATIONS

4.1 Monoamine Oxidase Inhibitors

VIIBRYD must not be used concomitantly in patients taking MAOIs or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions have been associated with symptoms that include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Allow at least 14 days after stopping VIIBRYD before starting an MAOI *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [*see Warnings and Precautions (5.6) and Dosage and Administration (2.4)*].

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as

the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for VIIBRYD should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose *[see also Patient Counseling Information (17.1)]*.

Screening patients for bipolar disorder
A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that VIIBRYD is not approved for use in treating bipolar depression.

5.2 Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions
The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions has been reported with antidepressants alone, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs that impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Symptoms of serotonin syndrome were noted in 0.1% of patients treated with VIIBRYD. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of VIIBRYD with MAOIs intended to treat depression is contraindicated. *[see Contraindications (4.1)]*.

If concomitant treatment of VIIBRYD with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Drug Interactions (7.1)]*.

The concomitant use of VIIBRYD with serotonin precursors (such as tryptophan) is not recommended *[see Drug Interactions (7.1)]*.

Treatment with VIIBRYD and any concomitant serotonergic (SSRI, serotonin–norepinephrine reuptake inhibitor [SNRI], triptan, buspirone, tramadol, etc.) or antidopaminergic drugs, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

5.3 Seizures
VIIBRYD has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from clinical studies. Like other antidepressants, VIIBRYD should be prescribed with caution in patients with a seizure disorder.

5.4 Abnormal Bleeding
The use of drugs that interfere with serotonin reuptake inhibition, including VIIBRYD, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of VIIBRYD and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.

5.5 Activation of Mania/Hypomania
Symptoms of mania/hypomania were reported in 0.1% of patients treated with VIIBRYD in clinical studies. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. As with all antidepressants, use VIIBRYD cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

5.6 Discontinuation of Treatment with VIIBRYD
There have been reports of adverse events occurring upon discontinuation of serotonergic antidepressants, particularly when discontinuation is abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Monitor patients for these symptoms when discontinuing VIIBRYD. Reduce the dose gradually whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, the dose may be decreased, but at a more gradual rate *[see Dosage and Administration, (2.4)]*.

5.7 Hyponatremia
Although no cases of hyponatremia resulting from VIIBRYD treatment were reported in the clinical studies, hyponatremia has occurred as a result of treatment with SSRIs and SNRIs. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk. Discontinuation of VIIBRYD in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience
The most commonly observed adverse reactions in VIIBRYD-treated MDD patients in placebo-controlled studies (incidence ≥ 5% and at least twice the rate of placebo) were: diarrhea, nausea, vomiting, and insomnia.

Patient Exposure

The safety of VIIBRYD was evaluated in 2,177 patients (18-70 years of age) diagnosed with MDD who participated in clinical studies, representing 552 patient-years of exposure. In an open-label 52 week study at 40 mg daily, 599 patients were exposed to VIIBRYD for a total of 348 patient-years.

The information presented in these sections was derived from studies of VIIBRYD 40 mg daily in major depressive disorder including: 1) 2 placebo-controlled 8-week studies in 861 patients, including 436 receiving vilazodone; and 2) an open-label 52-week study of 599 patients. These studies included a titration period of 10 mg daily for 7 days followed by 20 mg daily for 7 days. In these clinical trials, VIIBRYD was administered with food.

Because clinical trials are conducted under widely varying conditions and varying lengths of time, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect rates observed in practice.

Adverse reactions reported as reasons for discontinuation of treatment
In the placebo-controlled studies of MDD there was no single adverse reaction leading to discontinuation in > 1% of the patients. Overall, 7.1% of the patients who received VIIBRYD discontinued treatment due to an adverse reaction, compared with 3.2% of placebo-treated patients in these studies.

Common adverse reactions in placebo-controlled MDD studies
Table 2 shows the incidence of common adverse reactions that occurred in ≥ 2% of VIIBRYD-treated MDD patients (and greater than in placebo-treated patients) in the placebo-controlled studies.

Table 2: Common Adverse Reactions Occurring in ≥2% of VIIBRYD-treated Patients and > Placebo-treated Patients

System Organ Class Preferred Term	VIIBRYD 40 mg/day N = 436	Placebo N = 433
Gastrointestinal disorders		
Diarrhea	28	9
Nausea	23	5
Dry mouth	8	5
Vomiting	5	1
Dyspepsia	3	2
Flatulence	3	2
Gastroenteritis	3	<1
Nervous system disorders		
Dizziness	9	5
Somnolence	3	2
Paresthesia	3	1
Tremor	2	0
Psychiatric disorders		
Insomnia	6	2
Abnormal dreams	4	1
Libido decreased	4	<1
Restlessness *	3	<1
Orgasm abnormal**	3	0
General disorders		
Fatigue	4	3
Feeling jittery	2	<1
Cardiac disorders		
Palpitations	2	<1
Musculoskeletal and connective tissue disorders		
Arthralgia	3	2
Reproductive system and breast disorders		
Delayed ejaculation***	2	0
Erectile dysfunction***	2	1
Metabolism and nutrition disorders		

Increased appetite	2	1

*Includes restlessness, akathisia, and restless legs syndrome

**Includes orgasm abnormal and anorgasmia

***Male patients only (Placebo n=182; VIIBRYD n=170)

Table 3: Sexual Adverse Reactions: Percentage in the Placebo-Controlled Studies

	Males		Females	
Preferred Term	VIIBRYD N= 170	Placebo N= 182	VIIBRYD N=266	Placebo N=251
Decreased libido	5	0	3	<1
Abnormal orgasm*	4	0	2	0
Delayed ejaculation	2	0	–	–
Erectile dysfunction	2	1	–	–
Sexual dysfunction	2	0	<1	<1

– Not applicable
*Includes anorgasmia

Laboratory Tests
VIIBRYD has not been associated with any clinically important changes in laboratory test parameters in serum chemistry (including liver function tests), hematology and urinalysis, as measured in placebo-controlled studies. These studies include analysis of (1) mean change from baseline and (2) the proportion of patients meeting criteria for potentially clinically significant changes from baseline. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies.

ECG
VIIBRYD has not been associated with any clinically significant effect on ECG parameters, including QT, QTc, PR and QRS intervals, or with any arrhythmogenic potential. ECGs were evaluated in a thorough QTc study at doses up to 80 mg daily with food and in the placebo-controlled studies *[see Pharmacodynamics (12.2)]*.

Vital Signs
VIIBRYD has not been associated with any clinically significant effect on vital signs, including systolic and diastolic blood pressure and heart rate, as measured in placebo-controlled studies. These studies included analyses of (1) change from baseline, and (2) the proportion of patients meeting criteria for potentially clinically significant changes from baseline. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies.

Weight
VIIBRYD had no effect on body weight as measured by the mean change from baseline in the 8-week, placebo-controlled studies. The mean changes in weight were +0.16 kg in the VIIBRYD group and +0.18 kg in the placebo group. The proportions of patients with a weight gain $\geq$ 7% were 0.9% in the VIIBRYD group and 1.2% in the placebo group. The proportions of patients with a weight decrease $\geq$ 7% were 1.4% in the VIIBRYD group and 1.4% in the placebo group.

Other adverse reactions observed in clinical studies
The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: *frequent* adverse reactions are those occurring in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare* reactions are those occurring in fewer than 1/1000 patients:

Cardiac disorders: *infrequent*: ventricular extrasystoles

Eye disorders: *frequent:* vision blurred, dry eye; *infrequent:* cataracts

General disorders: *infrequent*: feeling abnormal

Metabolism and nutrition disorders: *frequent*: decreased appetite

Nervous System: *frequent*: sedation, migraine; *infrequent*: dysgeusia

Psychiatric disorders: *infrequent*: panic attack, mania

Renal and Urinary disorder: *infrequent*: pollakiuria

Skin and subcutaneous tissue disorders: *frequent*: hyperhidrosis, night sweats

7 DRUG INTERACTIONS

7.1 Central Nervous System (CNS)-Active Agents
The risk of using VIIBRYD in combination with other CNS-active drugs has not been systematically evaluated. Consequently, use caution when VIIBRYD is prescribed in combination with other CNS-active drugs.

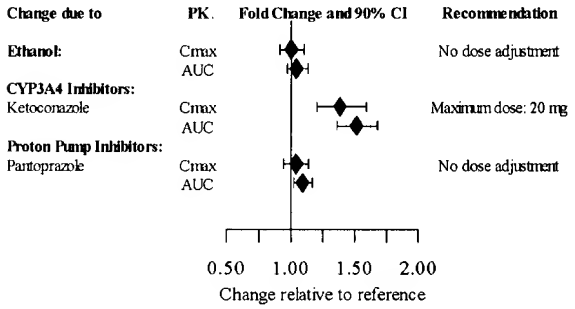
Monoamine Oxidase Inhibitors (MAOI)
Adverse reactions, some of which are serious or fatal, can develop in patients who use MAOIs or who have recently been discontinued from a MAOI and started on antidepressant(s) with pharmacological properties similar to VIIBRYD (e.g. SSRIs), or who have recently had SSRI therapy discontinued prior to initiation of an MAOI. Do not prescribe VIIBRYD concomitantly with an MAOI or within 14 days of discontinuing or starting an MAOI *[see Contraindications (4.1)]*.

Serotonergic Drugs
Based on the mechanism of action of VIIBRYD and the potential for serotonin toxicity, also known as serotonin syndrome, caution is advised when VIIBRYD is coadministered with other drugs that may affect the serotonergic neurotransmitter systems (e.g., MAOI, SSRIs, SNRIs, triptans, buspirone, tramadol, and tryptophan products etc.) *[see Warnings and Precautions (5.2)]*.

7.2 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when VIIBRYD is initiated or discontinued *[see Abnormal Bleeding (5.4)]*.

7.3 Potential for Other Drugs to Affect Vilazodone

Figure 1. Impact of other drugs on Vilazodone PK



Inhibitors of CYP3A4
Metabolism by CYP3A4 is a major elimination pathway for vilazodone. Concomitant use of VIIBRYD and strong inhibitors of CYP3A4 (e.g., ketoconazole) can increase vilazodone plasma concentrations by approximately 50% (see Figure 1). The VIIBRYD dose should be reduced to 20 mg if co-administered with a strong inhibitor of CYP3A4. During co-administration with moderate inhibitors of CYP3A4 (e.g., erythromycin), the VIIBRYD dose should be reduced to 20 mg for patients with intolerable adverse events. No dose adjustment is recommended when VIIBRYD is co-administered with mild inhibitors of CYP3A4 (e.g., cimetidine).

Inducers of CYP3A4
Concomitant use of VIIBRYD with inducers of CYP3A4 has the potential to reduce vilazodone systemic exposure. However, the effect of CYP3A4 inducers on vilazodone plasma concentrations has not been evaluated.

Inhibitors of other CYP enzymes
Concomitant administration of VIIBRYD with inhibitors of CYP2C19 and CYP2D6 is not expected to alter plasma concentrations of vilazodone. These isoforms are minor elimination pathways in the metabolism of vilazodone. *In vitro* studies have shown that CYP1A2, CYP2A6, CYP2C9 and CYP2E1 have minimal contribution to the metabolism of vilazodone.

7.4 Potential for Vilazodone to Affect Other Drugs

Drugs metabolized by CYP1A2, CYP2C9, CYP2D6, CYP3A4 or CYP2C19.
Coadministration of VIIBRYD with substrates for CYP1A2, CYP2C9, CYP3A4, or CYP2D6 is unlikely to result in clinically significant changes in the concentrations of the CYP substrates. A study in healthy subjects found that VIIBRYD (20 mg/day for 8-10 days) had no effect on the pharmacokinetics of caffeine, flurbiprofen, nifedipine or debrisoquine, probes for CYP1A2, CYP2C9, CYP3A4, and CYP2D6, respectively. VIIBRYD coadministration with mephenytoin to healthy subjects resulted in a small (11%) increase in mephenytoin biotransformation, suggestive of a minor induction of CYP2C19. *In vitro* studies have shown that VIIBRYD is a moderate inhibitor of CYP2C19 and CYP2D6.

Drugs metabolized by CYP2C8
Coadministration of VIIBRYD with a CYP2C8 substrate may lead to an increase in concentration of the other drug. *In vitro* studies suggest that VIIBRYD may inhibit the biotransformation of substrates of CYP2C8. The effect of VIIBRYD on CYP2C8 activity has not been tested *in vivo*.

Induction of CYP isoforms
VIIBRYD did not induce CYP1A1, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4 or 3A5 in an *in vitro* study in cultured human hepatocytes. Chronic administration of vilazodone is unlikely to induce the metabolism of drugs metabolized by these major CYP isoforms.

7.5 Drugs Highly Bound to Plasma Protein
The interaction between vilazodone and other highly protein-bound drugs has not been evaluated. Because vilazodone is highly bound to plasma protein, administration of VIIBRYD to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects
Pregnancy Category C

Vilazodone caused some developmental toxicity in rats, but was not teratogenic in rats or rabbits. There are no adequate and well-controlled studies of VIIBRYD in pregnant women. When treating pregnant women with VIIBRYD, carefully consider whether the potential benefits outweigh the potential risks of treatment.

No teratogenic effects were observed when vilazodone was given to pregnant rats or rabbits during the period of organogenesis at oral doses up to 200 and 36 mg/kg/day, respectively. These doses are 48 and 17 times, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 40 mg on a mg/m^2 basis. Fetal body weight gain was reduced, and skeletal ossification was delayed in both rats and rabbits at these doses; these effects were not observed at doses up to 10 times the MRHD in rats or 4 times the MRHD in rabbits.

When vilazodone was administered to pregnant rats at an oral dose of 30 times the MRHD during the period of organogenesis and throughout pregnancy and lactation, the number of live born pups was decreased. There was an increase in early postnatal pup mortality, and among surviving pups there was decreased body weight, delayed maturation, and decreased fertility in adulthood. There was some maternal toxicity at this dose. These effects were not seen at 6 times the MRHD.

Nonteratogenic Effects
Neonates exposed to serotonergic antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of serotonergic antidepressants or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome *[see Warnings and Precautions (5.2)]*.

8.2 Labor and Delivery
The effect of VIIBRYD on labor and delivery in humans is unknown. VIIBRYD should be used during labor and delivery only if the potential benefit outweighs the potential risk.

8.3 Nursing Mothers
Vilazodone is excreted into the milk of lactating rats. The effect of VIIBRYD on lactation and nursing in humans is unknown. Breast feeding in women treated with VIIBRYD should be considered only if the potential benefit outweighs the potential risk to the child.

8.4 Pediatric Use
Clinical studies on the use of VIIBRYD in pediatric patients have not been conducted; therefore, the safety and effectiveness of VIIBRYD in the pediatric population have not been established. VIIBRYD is not approved for use in pediatric patients *[see Box Warning and Warnings and Precautions (5.1)]*.

8.5 Geriatric Use
No dose adjustment is recommended on the basis of age (see Figure 2). Results from a single-dose (20 mg) pharmacokinetic study in elderly (> 65 years-old) vs. young (24-55 years-old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups.

Of the 2177 patients in clinical studies with VIIBRYD, 37 (1.7%) were 65 years of age or older, and 272 (12.5%) were 55 to 64 years of age.

Greater sensitivity of some older individuals cannot be ruled out *[see Dosage and Administration (2.3)]*.

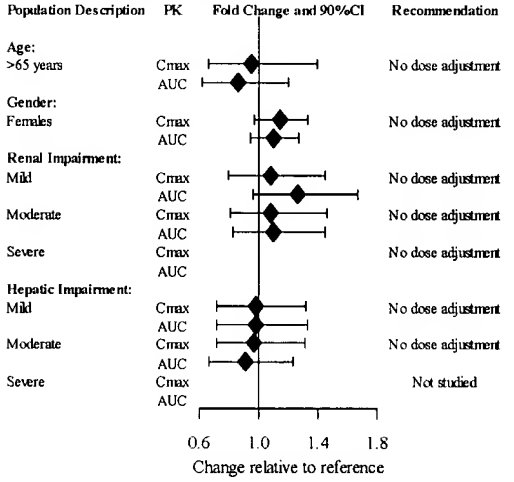
Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions (5.7)]*.

8.6 Hepatic Impairment
Vilazodone is eliminated primarily by hepatic metabolism. In mild and moderate hepatic impairment, no dose adjustment is necessary (see Figure 2). VIIBRYD has not been studied in patients with severe hepatic impairment *[see Dosage and Administration (2.3)]*.

8.7 Renal Impairment
In mild, moderate, and severe renal impairment, no dose adjustment is necessary (see Figure 2 below) *[see Dosage and Administration (2.3)]*.

8.8 Gender Effect
After adjustment for body weight, the systemic exposures between males and females are similar (see Figure 2).

Figure 2. Impact of Intrinsic Factors on Vilazodone PK



The data shown for elderly subjects (>65 years) are relative to younger subjects (24-55 y
The data shown for female subjects are relative to male subjects.
The data shown for renal and hepatic impairment are relative to subjects with normal renal and hepatic function, respectively.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
VIIBRYD is not a controlled substance.

9.2 Abuse and Dependence
VIIBRYD has been systematically studied in animals and did not demonstrate abuse or dependence potential. While VIIBRYD has not been systematically studied in humans for its potential for abuse, there was no suggested evidence of drug-seeking behavior in the clinical studies. However, it is not possible to predict on the basis of clinical experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of VIIBRYD (e.g., development of tolerance, drug-seeking behavior, increases in dose).

10 OVERDOSAGE

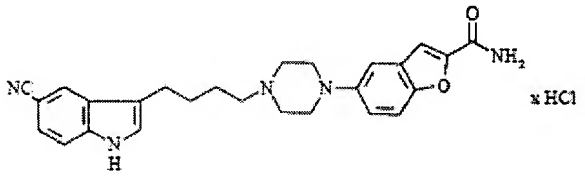
10.1 Human Experience
There is limited clinical experience regarding human overdosage with VIIBRYD. Four patients and 1 patient's child experienced an overdose of VIIBRYD; all recovered. The adverse reactions associated with overdose of VIIBRYD at doses of 200-280 mg as observed in clinical trials included serotonin syndrome, lethargy, restlessness, hallucinations, and disorientation.

10.2 Management of Overdose

Consult a Certified Poison Control Center for up-to-date guidance and advice. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). No specific antidotes for vilazodone are known. In case of an overdose, provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be considered. Removal of vilazodone by dialysis has not been studied; however, the high volume of distribution of vilazodone suggests that dialysis will not be effective in reducing vilazodone plasma concentrations.

11 DESCRIPTION
VIIBRYD Tablets for oral administration contain polymorph Form IV vilazodone hydrochloride (HCl), a selective serotonin reuptake inhibitor and a $5HT_{1A}$ receptor partial agonist.

Vilazodone HCl is 2-benzofurancarboxamide, 5-[4-[4-(5-cyano-1*H*-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1). Its molecular weight is 477.99. The structural formula is:



In addition to the active ingredient, VIIBRYD Tablets contain lactose monohydrate, microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C Blue #1 (40 mg only), FD&C Yellow #6 (20 mg only) and FD&C Red #40 (10 mg only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action
The mechanism of the antidepressant effect of vilazodone is not fully understood but is thought to be related to its enhancement of serotonergic activity in the CNS through selective inhibition of serotonin reuptake. Vilazodone is also a partial agonist at serotonergic $5\text{-}HT_{1A}$ receptors; however, the net result of this action on serotonergic transmission and its role in vilazodone's antidepressant effect are unknown.

12.2 Pharmacodynamics
Vilazodone binds with high affinity to the serotonin reuptake site (Ki= 0.1 nM), but not to the norepinephrine (Ki=56 nM) or dopamine (Ki=37 nM) reuptake sites. Vilazodone potently and selectively inhibits reuptake of serotonin (IC_{50}= 1.6 nM). Vilazodone also binds selectively with high affinity to $5\text{-}HT_{1A}$ receptors (IC_{50}=2.1 nM) and is a $5\text{-}HT_{1A}$ receptor partial agonist.

Thorough QT Study: Treatment with VIIBRYD did not prolong the QTc interval. The effect of vilazodone (20, 40, 60, and 80 mg) on the QTc interval was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg), parallel-group, thorough QTc study in 157 healthy subjects. The study demonstrated an ability to detect small effects. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc interval was below 10 msec, based on the individual correction method (QTcI). This is below the threshold for clinical concern. However, it is unknown whether 80 mg is adequate to represent a high clinical exposure condition.

12.3 Pharmacokinetics
Vilazodone activity is due primarily to the parent drug. The pharmacokinetics of vilazodone (5 mg – 80 mg) are dose-proportional. Accumulation of vilazodone is predictable from single dose data, does not vary with dose, and steady-state is achieved in about 3 days. Elimination of vilazodone is primarily by hepatic metabolism with a terminal half-life of approximately 25 hours. At steady-state, after daily dosing of VIIBRYD 40 mg under fed conditions, the mean C_{max} value is 156 ng/mL, and the mean AUC ($_{0\text{-}24\ hours}$) value is 1645 ng·h/mL.

Absorption
Vilazodone concentrations peak at a median of 4-5 hours (T_{max}) after administration and decline with a terminal half-life of approximately 25 hours. The absolute bioavailability of vilazodone is 72% with food. Administration of VIIBRYD with food (high fat or light meal) increases oral bioavailability (C_{max} increased by approximately 147-160%, and AUC increased by approximately 64-85%).

Coadministration of VIIBRYD with ethanol or with a proton pump inhibitor (pantoprazole) did not affect the rate or extent of vilazodone absorption [*see Drug Interactions (7.3, Figure 1)*]. In addition, neither the T_{max} nor terminal elimination rate of vilazodone was altered by coadministration with either pantoprazole or ethanol.

Absorption is decreased by approximately 25% if vomiting occurs within 7 hours of ingestion; no replacement dose is needed.

Distribution
Vilazodone is widely distributed and approximately 96-99% protein-bound

Metabolism and Elimination
VIIBRYD is extensively metabolized through CYP and non-CYP pathways (possibly by carboxylesterase), with only 1% of the dose recovered in the urine and 2% of the dose recovered in the feces as unchanged vilazodone. CYP3A4 is primarily responsible for its metabolism among CYP pathways, with minor contributions from CYP2C19 and CYP2D6. *In vitro* studies with human microsomes and human hepatocytes indicate that vilazodone is unlikely to inhibit or induce the metabolism of other CYP (except for CYP2C8) substrates; and an *in vivo* study with probe substrates for CYP2C19, 2D6 and 3A4 showed vilazodone did not alter the pharmacokinetics of the probe substrates. However, an *in vivo* study with probe substrate for CYP2C19 demonstrated a minor induction of CYP2C19. Strong inhibitors of CYP3A4 (e.g., ketoconazole) can reduce the metabolism of vilazodone *in vivo* and increase exposure. Conversely, inducers of CYP3A4 can decrease vilazodone exposure *[see Drug Interactions (7.3)]*.

The presence of mild or moderate renal impairment, or mild or moderate hepatic impairment did not affect the apparent clearance of vilazodone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Carcinogenicity studies were conducted in which B6C3F1mice and Wistar rats were given oral doses of vilazodone up to 135 and 150 mg/kg/day, respectively, for 2 years. These doses are approximately 16.5 and 36 times the maximum recommended human dose (MRHD) of 40 mg, respectively, on a mg/m^2 basis.

In mice, the incidence of hepatocellular carcinomas was increased in males at 16.5 times the MRHD; this finding was not observed at 5.5 times the MRHD. The incidence of malignant mammary gland tumors was numerically increased in females at 5.5 and 16.5 times the MRHD, with statistical significance at 16.5 the MHRD; this finding was not observed at 1.8 times the MRHD. Elevated prolactin levels were observed in a 2-week study of vilazodone administered at 5.5 and 33 times the MRHD. Increases in prolactin levels are known to cause mammary tumors in rodents.

In the rat study, vilazodone was not carcinogenic in either sex at doses up to 36 times the MRHD.

Mutagenesis
Vilazodone was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test). Vilazodone was negative in the *in vitro* V79/HGRPT mammalian cell forward mutation assay. Vilazodone was clastogenic in two *in vitro* mammalian cell chromosome aberration assays. However, vilazodone was negative for clastogenic activity in both an *in vivo* rat bone marrow chromosome aberration assay and a micronucleus test. Vilazodone was also negative in an *in vivo/in vitro* unscheduled DNA synthesis assay in rats.

Impairment of Fertility
Treatment of rats with vilazodone at a dose of 125 mg/kg, which is 30 times the maximum recommended human dose (MRHD) of 40 mg on a mg/m^2 basis, caused impairment of male fertility with no effect on female fertility. Impaired male fertility was not observed at 6 times the MRHD.

14 CLINICAL STUDIES
The efficacy of VIIBRYD as a treatment for major depressive disorder was established in two 8-week, multicenter, randomized, double-blind, placebo-controlled studies in adult (18-70 years of age) outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for MDD. In these studies, patients were titrated over 2 weeks to a dose of 40 mg of VIIBRYD with food (n=436) or placebo (n = 433) once daily. VIIBRYD was superior to placebo in the improvement of depressive symptoms as measured by the mean change from baseline to Week 8 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. Examination of population subgroups based on age (there were few patients over 65), gender, and race did not reveal any clear evidence of differential responsiveness.

Table 4. Summary of Results for the Primary Efficacy Endpoint

Study Number	Primary Endpoint	LS Mean (95% CI) [a] difference from placebo in change from baseline
1	MADRS	-3.2 (-5.2, -1.3)
2	MADRS	-2.5 (-4.4, -0.6)

[a] Least Squares Mean (95% Confidence Interval)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
VIIBRYD (vilazodone HCl) Tablets are supplied in the following configurations:
10 mg, pink, oval tablet, debossed with 10 on one side
75838-110-30: 30-count bottles
75838-110-90: 90-count bottles
75838-110-52: 500-count bottles
75838-110-12: 10 blisters cards each containing 10 tablets (HUD)

20 mg, orange, oval tablet, debossed with 20 on one side
75838-120-30: 30-count bottles
75838-120-90: 90-count bottles

75838-120-52: 500-count bottles
75838-120-12: 10 blisters cards each containing 10 tablets (HUD)

40 mg, blue, oval tablet, debossed with 40 on one side
75838-140-30: 30-count bottles
75838-140-90: 90-count bottles
75838-140-52: 500-count bottles
75838-140-12: 10 blisters cards each containing 10 tablets (HUD)

Patient Starter Kit
75838-179-30: blister card containing 30 tablets:
10 mg, pink, oval, debossed with 10 on one side: 7 tablets
20 mg, orange, oval, debossed with 20 on one side: 7 tablets
40 mg, blue, oval, debossed with 40 on one side: 16 tablets

16.2 Storage
VIIBRYD (vilazodone HCl) Tablets should be stored at 25°C (77°F) with excursions permitted to 15°C - 30°C (59°F - 86°F) [*see USP Controlled Room Temperature*].

17 PATIENT COUNSELING INFORMATION
See Medication Guide (17.2).

17.1 Information for Patients
Advise patients and their caregivers about the benefits and risks associated with treatment with VIIBRYD and counsel them in its appropriate use. Advise patients and their caregivers to read the Medication Guide and assist them in understanding its contents. The complete text of the Medication Guide is reprinted at the end of this document.

Suicide Risk
Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dose is adjusted up or down [*see Box Warning and Warnings and Precautions (5.1)*].

Dosing and Administration
Instruct patients to take VIIBRYD with food. When initiating treatment with VIIBRYD the dose should be titrated, starting with a dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then increased to 40 mg once daily.

Concomitant Medication
Instruct patients not to take VIIBRYD with an MAOI or within 14 days of stopping an MAOI and to allow 14 days after stopping VIIBRYD before starting an MAOI [*see Contraindications (4.1)*].

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions
Caution patients about the risk of serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions, particularly with the concomitant use of VIIBRYD and triptans, tramadol, tryptophan supplements, other serotonergic agents, or antipsychotic drugs [*see Warnings and Precautions (5.2) and Drug Interactions (7.1)*].

Seizures
Caution patients about using VIIBRYD if they have a history of a seizure disorder [*see Warnings and Precautions (5.3)*]. Patients with a history of seizures were excluded from clinical studies.

Abnormal Bleeding
Caution patients about the concomitant use of VIIBRYD and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of abnormal bleeding [*see Warnings and Precautions (5.4)*].

Activation of Mania/Hypomania
Advise patients and their caregivers to observe for signs of activation of mania/hypomania [*see Warnings and Precautions (5.5)*].

Discontinuation
Advise patients not to stop taking VIIBRYD without talking first with their healthcare provider. Patients should be aware that discontinuation effects may occur when suddenly stopping VIIBRYD [*see Warnings and Precautions (5.6)*].

Hyponatremia
Advise patients that if they are treated with diuretics, or are otherwise volume depleted, or are elderly, they may be at greater risk of developing hyponatremia while taking VIIBRYD [*see Warnings and Precautions (5.7)*].

Alcohol
Advise patients to avoid alcohol while taking VIIBRYD [*see Drug Interactions (7.3)*].

Allergic Reactions
Advise patients to notify their healthcare provider if they develop an allergic reaction such as rash, hives, swelling, or difficulty breathing.

Pregnancy
Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy with VIIBRYD [*see Use in Specific Populations (8.1)*].

Nursing Mothers
Advise patients to notify their healthcare provider if they are breastfeeding an infant and would like to continue or start VIIBRYD [*see Use in Specific Populations (8.3)*].

Interference with Cognitive and Motor Performance

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that VIIBRYD therapy does not adversely affect their ability to engage in such activities.

TROVIS PHARMACEUTICALS

Distributed by
Trovis Pharmaceuticals LLC
New Haven, CT 06511

877-878-7200
viibryd.com

Licensed from Merck KGaA,
Darmstadt, Germany

Product protected by U.S. Patent No. 5,532,241 and U.S. Patent No. 7,834,020.

VZ59PI0000
Revised: January 2010

EXHIBIT 6

NDA Approval Letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022567

NDA APPROVAL

Trovis Pharmaceuticals LLC
Attention: Kimberly Fabrizio
Vice President, Regulatory Affairs
Five Science Park
New Haven, CT 06511

Dear Ms. Fabrizio:

Please refer to your New Drug Application (NDA) dated March 22, 2010, received March 22, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Viibryd (vilazodone hydrochloride) 10 mg, 20 mg, and 40 mg tablets.

We acknowledge receipt of your amendments dated May 4, 2010, May 7, 2010, May 18, 2010, May 19, 2010, May 25, 2010, June 3, 2010, June 8, 2010, June 30, 2010, August 4, 2010, August 19, 2010, August 23, 2010, August 31, 2010, September 27, 2010, November 4, 2010, November 18, 2010, November 30, 2010, December 3, 2010, December 13, 2010, December 15, 2010, December 23, 2010, December 29, 2010, January 4, 2011, January 6, 2011, January 7, 2011, January 11, 2011, and January 13, 2011.

This new drug application provides for the use of Viibryd (vilazodone hydrochloride) for the treatment of Major Depressive Disorder.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.
The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels as agreed upon in our January 14, 2011 communication as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22567**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for vilazodone was not referred to an FDA advisory committee because this drug is not the first in its class, and the safety profile is similar to that of other drugs approved for this indication.

PROPRIETARY NAME

The Division of Medication Error and Prevention and Analysis (DMEPA) and the Division of Psychiatry Products do not object to the use of the proprietary name, Viibryd, for this product.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 6 years old in the treatment of major depressive disorder, because studies are highly impractical due to the low prevalence of this disorder in this age range.

We are deferring submission of your pediatric studies for ages 7 to 17 years old in the treatment of major depressive disorder, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

1723-1 Deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients aged 7 to 17. Conduct a study to obtain pharmacokinetic, safety, and tolerability data and provide information pertinent to dosing of vilazodone in the relevant pediatric population.

Final Protocol Submission Date:	January 31, 2012
Study Completion Date:	February 28, 2013
Final Report Submission:	January 31, 2016

1723-2 Deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients aged 7 to 17. Conduct a study to obtain data on the efficacy and safety of vilazodone in the relevant pediatric population. This must be a placebo-controlled and active-controlled (fluoxetine) study. This study must be a fixed-dose study.

Final Protocol Submission Date:	May 31, 2013
Study Completion Date:	July 31, 2015
Final Report Submission:	January 31, 2016

1723-3 Deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients aged 7 to 17. Conduct a second study to obtain data on the efficacy and safety of vilazodone in the relevant pediatric population. This must be a placebo-controlled and active-controlled (fluoxetine) study. This study may be a fixed-dose study.

Final Protocol Submission Date:	May 31, 2013
Study Completion Date:	July 31, 2015
Final Report Submission:	January 31, 2016

1723-4 To support the use of vilazodone in children less than 13 years of age, you must conduct a study to assess the safety of vilazodone in juvenile rats. This study must include evaluation of neurological/behavioral development and reproductive development. You should submit the protocol for our comments prior to initiating the study.

Final Protocol Submission Date:	January 30, 2012

Study Completion Date:	January 30, 2014
Final Report Submission:	January 30, 2015

Submit final reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment(s).**"

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

The major human metabolite of vilazodone, M17, was not demonstrated to be present in plasma of either rats or rabbits. Therefore the embryo-fetal reproductive toxicity studies with vilazodone did not adequately assess the potential reproductive toxicity of M17.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the reproductive toxicity of the major human metabolite M17.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1723-5 Assess the reproductive toxicity of metabolite M17 by conducting an embryo-fetal study in either rats or rabbits in which M17 is administered by a route that will produce systemic exposure equal to or greater than the exposure in humans at the maximum recommended human dose (MRHD).

The timetable, as agreed upon on a January 19, 2011 communication, states that you will conduct this study according to the following schedule:

Final Protocol Submission Date:	Not applicable
Study Completion Date:	November 30, 2012
Final Report Submission:	January 31, 2013

1723-6 Assess the reproductive toxicity of metabolite M17 by demonstrating that the original rabbit study was adequate to assess the embryo-fetal toxicity of M17. This will require data demonstrating that the systemic exposure to M17 in rabbits in that study was equal to or greater than that in humans at the MRHD.

The timetable, as agreed upon on a January 19, 2011 communication, states that you will conduct this study according to the following schedule:

Final Protocol Submission Date:	Not applicable
Study Completion Date:	November 30, 2012
Final Report Submission:	January 31, 2013

If you are able to address postmarketing study 1723-6 adequately through analyses of existing data, FDA may release you from postmarketing study 1723-5.

Submit the protocol to your IND 54613, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments agreed upon in your communications dated January 19, 2011:

1723-7 A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of vilazodone in the treatment of adults with major depressive disorder. This trial must be placebo-controlled, utilize a randomized withdrawal design, and include an adequate period of stabilization with open-label treatment of vilazodone prior to double-blind randomization.

Final Protocol Submission:	September 30, 2011
Trial Completion Date:	January 31, 2015
Final Report Submission:	January 31, 2016

1723-8 It is not apparent from the trials you have conducted in major depressive disorder that the lowest effective dose of vilazodone has been identified, because only one dose (40 mg/day) was studied. However, there are suggestions that 20 mg/day may be effective at least in some subjects. In one of the trials, those who did not tolerate 40 mg/day could continue in the trial on a dose of 20 mg/day, and some may have had a significant treatment effect. In addition, data from the phase 2 fixed-dose trials suggest that there may have been a signal of efficacy with the 20 mg/day dose, as measured by the secondary efficacy measure (MADRS). Moreover, some important adverse reactions are dose-related. Thus, we request that you further characterize the efficacy and safety of vilazodone in the treatment of adults with MDD using fixed doses of vilazodone (20 mg and 40 mg), an active control (for assay sensitivity), and placebo in an adequate and well controlled trial.

Final Protocol Submission:	October 31, 2011
Trial Completion:	January 31, 2013
Final Report Submission:	January 31, 2014

1723-9 Vilazodone is metabolized primarily by CYP3A4. You have not submitted information on the potential effect of CYP3A4 induction on vilazodone exposure. We request that you conduct a drug-drug interaction trial of vilazodone using a CYP3A4 inducer (carbamazepine) in healthy subjects.

Final Protocol Submission:	July 31, 2011
Trial Completion:	July 31, 2012
Final Report Submission:	January 31, 2013

1723-10 Vilazodone is extensively metabolized; however, the pharmacokinetics of vilazodone in patients with severe hepatic impairment has not been assessed. We request that you conduct a Phase 1 trial to evaluate the pharmacokinetics of vilazodone in patients with severe hepatic impairment.

Final Protocol Submission:	July 31, 2011
Trial Completion:	July 31, 2012
Final Report Submission:	February 28, 2013

1723-11 Information on the effect of PgP on the pharmacokinetics of vilazodone and the effect of vilazodone on PgP was not submitted. We request that you conduct an *in vitro* study to evaluate whether vilazodone is a substrate or inhibitor of PgP.

Final Protocol Submission:	July 31, 2011
Study Completion:	September 30, 2011
Final Report Submission:	December 31, 2011

Submit clinical protocols to your IND 54613 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under

21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirement were outlined in our REMS notification letter dated November 1, 2010.

Your proposed REMS, submitted on December 15, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

a. An evaluation of patients' understanding of the serious risks of Viibryd (vilazodone hydrochloride) Tablets.
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to

the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22567 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 22567
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 22567
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

Please submit one market package of the drug product when it is available.

DISSOLUTION METHOD AND SPECIFICATIONS

The dissolution method test conditions for all tablet strengths (10 mg, 20 mg, and 40 mg) are as follows:

USP Apparatus: 2 (Paddle) x 60 rpm
Medium: 0.1% Acetic Acid (pH 3.1), 1000 mL at 37°C
Specifications: Q=80% at 30 min

EXPIRY DATE

A 24 month expiry date is granted based on the available stability data.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, email CDR Bill Bender, Senior Regulatory Project Manager, at william.bender@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ellis Unger, M.D.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
REMS

VIIBRYD™ (vilazodone hydrochloride) Tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VIIBRYD™ safely and effectively. See full prescribing information for VIIBRYD.

VIIBRYD (vilazodone HCl) Tablets for oral administration
Initial U.S. Approval: 2011

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

See full prescribing information for complete boxed warning.
Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders (5.1).
VIIBRYD is not approved for use in pediatric patients (8.4).

INDICATIONS AND USAGE

VIIBRYD is indicated for the treatment of major depressive disorder (MDD). The efficacy of VIIBRYD was established in two 8-week, placebo-controlled trials in adult patients with MDD (1, 14).

DOSAGE AND ADMINISTRATION

- The recommended dose for VIIBRYD is 40 mg once daily (2).
- VIIBRYD should be titrated to the 40 mg dose, starting with an initial dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then increased to 40 mg once daily (2).
- VIIBRYD should be taken with food. Administration without food can result in inadequate drug concentrations and may diminish effectiveness (2, 12.3).
- When discontinuing treatment, reduce the dose gradually (2.4).

DOSAGE FORMS AND STRENGTHS

VIIBRYD is available as 10 mg, 20 mg and 40 mg tablets (3).

CONTRAINDICATIONS

- **Monoamine Oxidase Inhibitors**: Do not use VIIBRYD concomitantly with an MAOI or within 14 days of stopping or starting an MAOI (4.1).

WARNINGS AND PRECAUTIONS

Clinical Worsening/Suicide Risk: Monitor patients for clinical worsening and suicidal thinking or behavior (5.1).
Serotonin Syndrome or Neuroleptic Malignant (NMS)-like Syndrome: Can occur with treatment. Discontinue and initiate supportive treatment (5.2).
Seizures: Can occur with treatment. Use with caution in patients with a seizure disorder (5.3).
Abnormal Bleeding: Treatment can increase the risk of bleeding. Use with caution in association with nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or other drugs that affect coagulation (5.4).
Activation of Mania/Hypomania: Can occur with treatment. Screen patients for bipolar disorder (5.5).
Discontinuation of Treatment with VIIBRYD: A gradual reduction in dose is recommended rather than an abrupt cessation (5.6).
Hyponatremia: Can occur in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (5.7).

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) are: diarrhea, nausea, vomiting, and insomnia (6).
To report SUSPECTED ADVERSE REACTIONS, contact Trovis Pharmaceuticals at 1-877-878-7200 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

MAOIs: Do not use VIIBRYD concomitantly with an MAOI or within 14 days of stopping or starting an MAOI (4.1, 7.1).
CYP3A4 inhibitors: The VIIBRYD dose should be reduced to 20 mg when co-administered with CYP3A4 strong inhibitors (7.3).
CYP3A4 inducers: Concomitant use of VIIBRYD with inducers of CYP3A4 can result in inadequate drug concentrations and may diminish effectiveness. The effect of CYP3A4 inducers on systemic exposure of vilazodone has not been evaluated (7.3).

USE IN SPECIFIC POPULATIONS

Pregnancy: There are no controlled human data regarding VIIBRYD use during pregnancy. Use only if the potential benefits outweigh the potential risks (2.3, 8.1).
Nursing Mothers: There are no human data regarding VIIBRYD concentrations in breast milk. Women should breast feed only if the potential benefits outweigh the potential risks (8.3, 2.3).
Pediatric Use: The safety and efficacy of VIIBRYD in pediatric patients have not been studied (8.4).
Geriatric Use: No dose adjustment is recommended on the basis of age (8.5).
Hepatic Impairment: No dose adjustment is recommended in patients with mild or moderate hepatic impairment. VIIBRYD has not been studied in patients with severe hepatic impairment (8.6).
Renal Impairment: No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment. (8.7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: January 2010

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed**

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of VIIBRYD or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. VIIBRYD is not approved for use in pediatric patients [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4), and Patient Counseling Information (17.1)*]

1 INDICATIONS AND USAGE

VIIBRYD is indicated for the treatment of major depressive disorder (MDD). The efficacy of VIIBRYD was established in two 8-week, randomized, double-blind, placebo-controlled trials in adult patients with a diagnosis of MDD *[see Clinical Studies (14)]*.

Major depressive disorder consists of one or more major depressive episodes. A major depressive episode (DSM-IV-TR) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Treatment of Major Depressive Disorder

The recommended dose for VIIBRYD is 40 mg once daily. VIIBRYD should be titrated, starting with an initial dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then an increase to 40 mg once daily. VIIBRYD should be taken with food. VIIBRYD blood concentrations (AUC) in the fasted state can be decreased by approximately 50% compared to the fed state, and may result in diminished effectiveness in some patients *[see Pharmacokinetics (12.3)]*.

2.2 Maintenance/Continuation/Extended Treatment

The efficacy of VIIBRYD has not been systematically studied beyond 8 weeks. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Patients should be reassessed periodically to determine the need for maintenance treatment and the appropriate dose for treatment.

2.3 Dosing in Special Populations

Pregnant Women: Neonates exposed to serotonergic antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. When treating pregnant women with VIIBRYD, consider whether the potential benefits outweigh the potential risks of treatment *[see Pregnancy (8.1)]*.

Nursing Mothers: There are no clinical data regarding the effect of VIIBRYD on lactation and nursing *[see Nursing Mothers (8.3)]*. Breastfeeding in women treated with VIIBRYD should be considered only if the potential benefit outweighs the potential risk.

Pediatric Patients: The safety and efficacy of VIIBRYD have not been studied in pediatric patients *[see Pediatric Use (8.4)]*.

Geriatric Patients: No dose adjustment is recommended on the basis of age *[see Geriatric Use (8.5)]*.

Hepatic Impairment: No dose adjustment is recommended in patients with mild or moderate hepatic impairment. VIIBRYD has not been studied in severe hepatic impairment *[see Hepatic Impairment (8.6)]*.

Renal Impairment: No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment. *[see Renal Impairment (8.7)]*.

Gender: No dose adjustment is recommended on the basis of gender *[see Gender Effect (8.8)]*.

2.4 Discontinuing Treatment

Discontinuation symptoms have been reported with discontinuation of serotonergic drugs such as VIIBRYD. Gradual dose reduction is recommended, instead of abrupt discontinuation, whenever possible. Monitor patients for these symptoms when discontinuing VIIBRYD. If intolerable symptoms occur following a dose decrease or upon discontinuation of treatment, consider resuming the previously prescribed dose and decreasing the dose at a more gradual rate *[see Warnings and Precautions (5.6)]*.

2.5 Monoamine Oxidase Inhibitors (MAOI)

At least 14 days must elapse between discontinuation of an MAOI and initiation of therapy with VIIBRYD. In addition, at least 14 days must be allowed after stopping VIIBRYD before starting an MAOI *[see Contraindications (4.1)]*.

3 DOSAGE FORMS AND STRENGTHS

VIIBRYD Tablets are available as 10 mg, 20 mg and 40 mg immediate-release, film-coated tablets.
10 mg pink, oval tablet, debossed with 10 on one side
20 mg orange, oval tablet, debossed with 20 on one side
40 mg blue, oval tablet, debossed with 40 on one side

4 CONTRAINDICATIONS

4.1 Monoamine Oxidase Inhibitors

VIIBRYD must not be used concomitantly in patients taking MAOIs or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions have been associated with symptoms that include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Allow at least 14 days after stopping VIIBRYD before starting an MAOI *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [*see Warnings and Precautions (5.6) and Dosage and Administration (2.4)*].

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as

the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for VIIBRYD should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose *[see also Patient Counseling Information (17.1)]*.

Screening patients for bipolar disorder
A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that VIIBRYD is not approved for use in treating bipolar depression.

5.2 Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions
The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions has been reported with antidepressants alone, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs that impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Symptoms of serotonin syndrome were noted in 0.1% of patients treated with VIIBRYD. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of VIIBRYD with MAOIs intended to treat depression is contraindicated. *[see Contraindications (4.1)]*.

If concomitant treatment of VIIBRYD with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Drug Interactions (7.1)]*.

The concomitant use of VIIBRYD with serotonin precursors (such as tryptophan) is not recommended *[see Drug Interactions (7.1)]*.

Treatment with VIIBRYD and any concomitant serotonergic (SSRI, serotonin–norepinephrine reuptake inhibitor [SNRI], triptan, buspirone, tramadol, etc.) or antidopaminergic drugs, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

5.3 Seizures
VIIBRYD has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from clinical studies. Like other antidepressants, VIIBRYD should be prescribed with caution in patients with a seizure disorder.

5.4 Abnormal Bleeding
The use of drugs that interfere with serotonin reuptake inhibition, including VIIBRYD, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of VIIBRYD and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.

5.5 Activation of Mania/Hypomania
Symptoms of mania/hypomania were reported in 0.1% of patients treated with VIIBRYD in clinical studies. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. As with all antidepressants, use VIIBRYD cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

5.6 Discontinuation of Treatment with VIIBRYD
There have been reports of adverse events occurring upon discontinuation of serotonergic antidepressants, particularly when discontinuation is abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Monitor patients for these symptoms when discontinuing VIIBRYD. Reduce the dose gradually whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, the dose may be decreased, but at a more gradual rate *[see Dosage and Administration, (2.4)]*.

5.7 Hyponatremia
Although no cases of hyponatremia resulting from VIIBRYD treatment were reported in the clinical studies, hyponatremia has occurred as a result of treatment with SSRIs and SNRIs. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk. Discontinuation of VIIBRYD in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience
The most commonly observed adverse reactions in VIIBRYD-treated MDD patients in placebo-controlled studies (incidence ≥ 5% and at least twice the rate of placebo) were: diarrhea, nausea, vomiting, and insomnia.

Patient Exposure

The safety of VIIBRYD was evaluated in 2,177 patients (18-70 years of age) diagnosed with MDD who participated in clinical studies, representing 552 patient-years of exposure. In an open-label 52 week study at 40 mg daily, 599 patients were exposed to VIIBRYD for a total of 348 patient-years.

The information presented in these sections was derived from studies of VIIBRYD 40 mg daily in major depressive disorder including: 1) 2 placebo-controlled 8-week studies in 861 patients, including 436 receiving vilazodone; and 2) an open-label 52-week study of 599 patients. These studies included a titration period of 10 mg daily for 7 days followed by 20 mg daily for 7 days. In these clinical trials, VIIBRYD was administered with food.

Because clinical trials are conducted under widely varying conditions and varying lengths of time, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect rates observed in practice.

Adverse reactions reported as reasons for discontinuation of treatment
In the placebo-controlled studies of MDD there was no single adverse reaction leading to discontinuation in > 1% of the patients. Overall, 7.1% of the patients who received VIIBRYD discontinued treatment due to an adverse reaction, compared with 3.2% of placebo-treated patients in these studies.

Common adverse reactions in placebo-controlled MDD studies
Table 2 shows the incidence of common adverse reactions that occurred in ≥ 2% of VIIBRYD-treated MDD patients (and greater than in placebo-treated patients) in the placebo-controlled studies.

Table 2: Common Adverse Reactions Occurring in ≥2% of VIIBRYD-treated Patients and > Placebo-treated Patients

System Organ Class Preferred Term	VIIBRYD 40 mg/day N = 436	Placebo N = 433
Gastrointestinal disorders		
Diarrhea	28	9
Nausea	23	5
Dry mouth	8	5
Vomiting	5	1
Dyspepsia	3	2
Flatulence	3	2
Gastroenteritis	3	<1
Nervous system disorders		
Dizziness	9	5
Somnolence	3	2
Paresthesia	3	1
Tremor	2	0
Psychiatric disorders		
Insomnia	6	2
Abnormal dreams	4	1
Libido decreased	4	<1
Restlessness *	3	<1
Orgasm abnormal**	3	0
General disorders		
Fatigue	4	3
Feeling jittery	2	<1
Cardiac disorders		
Palpitations	2	<1
Musculoskeletal and connective tissue disorders		
Arthralgia	3	2
Reproductive system and breast disorders		
Delayed ejaculation***	2	0
Erectile dysfunction***	2	1
Metabolism and nutrition disorders		

Increased appetite	2	1

*Includes restlessness, akathisia, and restless legs syndrome

**Includes orgasm abnormal and anorgasmia

***Male patients only (Placebo n=182; VIIBRYD n=170)

Table 3: Sexual Adverse Reactions: Percentage in the Placebo-Controlled Studies

	Males		Females	
Preferred Term	VIIBRYD N= 170	Placebo N= 182	VIIBRYD N=266	Placebo N=251
Decreased libido	5	0	3	<1
Abnormal orgasm*	4	0	2	0
Delayed ejaculation	2	0	–	–
Erectile dysfunction	2	1	–	–
Sexual dysfunction	2	0	<1	<1

– Not applicable
*Includes anorgasmia

Laboratory Tests
VIIBRYD has not been associated with any clinically important changes in laboratory test parameters in serum chemistry (including liver function tests), hematology and urinalysis, as measured in placebo-controlled studies. These studies include analysis of (1) mean change from baseline and (2) the proportion of patients meeting criteria for potentially clinically significant changes from baseline. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies.

ECG
VIIBRYD has not been associated with any clinically significant effect on ECG parameters, including QT, QTc, PR and QRS intervals, or with any arrhythmogenic potential. ECGs were evaluated in a thorough QTc study at doses up to 80 mg daily with food and in the placebo-controlled studies *[see Pharmacodynamics (12.2)]*.

Vital Signs
VIIBRYD has not been associated with any clinically significant effect on vital signs, including systolic and diastolic blood pressure and heart rate, as measured in placebo-controlled studies. These studies included analyses of (1) change from baseline, and (2) the proportion of patients meeting criteria for potentially clinically significant changes from baseline. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies.

Weight
VIIBRYD had no effect on body weight as measured by the mean change from baseline in the 8-week, placebo-controlled studies. The mean changes in weight were +0.16 kg in the VIIBRYD group and +0.18 kg in the placebo group. The proportions of patients with a weight gain $\geq$ 7% were 0.9% in the VIIBRYD group and 1.2% in the placebo group. The proportions of patients with a weight decrease $\geq$ 7% were 1.4% in the VIIBRYD group and 1.4% in the placebo group.

Other adverse reactions observed in clinical studies
The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: *frequent* adverse reactions are those occurring in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare* reactions are those occurring in fewer than 1/1000 patients:

Cardiac disorders: *infrequent*: ventricular extrasystoles

Eye disorders: *frequent:* vision blurred, dry eye; *infrequent:* cataracts

General disorders: *infrequent*: feeling abnormal

Metabolism and nutrition disorders: *frequent*: decreased appetite

Nervous System: *frequent*: sedation, migraine; *infrequent*: dysgeusia

Psychiatric disorders: *infrequent*: panic attack, mania

Renal and Urinary disorder: *infrequent*: pollakiuria

Skin and subcutaneous tissue disorders: *frequent*: hyperhidrosis, night sweats

7 DRUG INTERACTIONS

7.1 Central Nervous System (CNS)-Active Agents
The risk of using VIIBRYD in combination with other CNS-active drugs has not been systematically evaluated. Consequently, use caution when VIIBRYD is prescribed in combination with other CNS-active drugs.

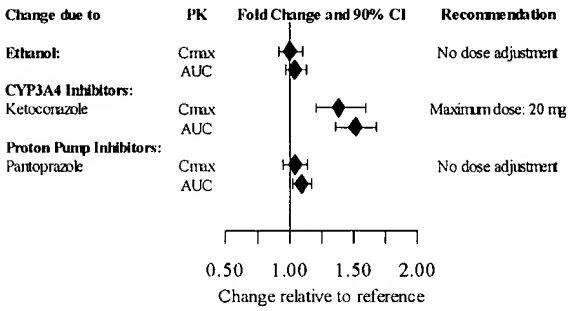
Monoamine Oxidase Inhibitors (MAOI)
Adverse reactions, some of which are serious or fatal, can develop in patients who use MAOIs or who have recently been discontinued from a MAOI and started on antidepressant(s) with pharmacological properties similar to VIIBRYD (e.g. SSRIs), or who have recently had SSRI therapy discontinued prior to initiation of an MAOI. Do not prescribe VIIBRYD concomitantly with an MAOI or within 14 days of discontinuing or starting an MAOI *[see Contraindications (4.1)]*.

Serotonergic Drugs
Based on the mechanism of action of VIIBRYD and the potential for serotonin toxicity, also known as serotonin syndrome, caution is advised when VIIBRYD is coadministered with other drugs that may affect the serotonergic neurotransmitter systems (e.g., MAOI, SSRIs, SNRIs, triptans, buspirone, tramadol, and tryptophan products etc.) *[see Warnings and Precautions (5.2)]*.

7.2 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when VIIBRYD is initiated or discontinued *[see Abnormal Bleeding (5.4)]*.

7.3 Potential for Other Drugs to Affect Vilazodone

Figure 1. Impact of other drugs on Vilazodone PK



Inhibitors of CYP3A4
Metabolism by CYP3A4 is a major elimination pathway for vilazodone. Concomitant use of VIIBRYD and strong inhibitors of CYP3A4 (e.g., ketoconazole) can increase vilazodone plasma concentrations by approximately 50% (see Figure 1). The VIIBRYD dose should be reduced to 20 mg if co-administered with a strong inhibitor of CYP3A4. During co-administration with moderate inhibitors of CYP3A4 (e.g., erythromycin), the VIIBRYD dose should be reduced to 20 mg for patients with intolerable adverse events. No dose adjustment is recommended when VIIBRYD is co-administered with mild inhibitors of CYP3A4 (e.g., cimetidine).

Inducers of CYP3A4
Concomitant use of VIIBRYD with inducers of CYP3A4 has the potential to reduce vilazodone systemic exposure. However, the effect of CYP3A4 inducers on vilazodone plasma concentrations has not been evaluated.

Inhibitors of other CYP enzymes
Concomitant administration of VIIBRYD with inhibitors of CYP2C19 and CYP2D6 is not expected to alter plasma concentrations of vilazodone. These isoforms are minor elimination pathways in the metabolism of vilazodone. *In vitro* studies have shown that CYP1A2, CYP2A6, CYP2C9 and CYP2E1 have minimal contribution to the metabolism of vilazodone.

7.4 Potential for Vilazodone to Affect Other Drugs

Drugs metabolized by CYP1A2, CYP2C9, CYP2D6, CYP3A4 or CYP2C19.
Coadministration of VIIBRYD with substrates for CYP1A2, CYP2C9, CYP3A4, or CYP2D6 is unlikely to result in clinically significant changes in the concentrations of the CYP substrates. A study in healthy subjects found that VIIBRYD (20 mg/day for 8-10 days) had no effect on the pharmacokinetics of caffeine, flurbiprofen, nifedipine or debrisoquine, probes for CYP1A2, CYP2C9, CYP3A4, and CYP2D6, respectively. VIIBRYD coadministration with mephenytoin to healthy subjects resulted in a small (11%) increase in mephenytoin biotransformation, suggestive of a minor induction of CYP2C19. *In vitro* studies have shown that VIIBRYD is a moderate inhibitor of CYP2C19 and CYP2D6.

Drugs metabolized by CYP2C8
Coadministration of VIIBRYD with a CYP2C8 substrate may lead to an increase in concentration of the other drug. *In vitro* studies suggest that VIIBRYD may inhibit the biotransformation of substrates of CYP2C8. The effect of VIIBRYD on CYP2C8 activity has not been tested *in vivo*.

Induction of CYP isoforms
VIIBRYD did not induce CYP1A1, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4 or 3A5 in an *in vitro* study in cultured human hepatocytes. Chronic administration of vilazodone is unlikely to induce the metabolism of drugs metabolized by these major CYP isoforms.

7.5 Drugs Highly Bound to Plasma Protein
The interaction between vilazodone and other highly protein-bound drugs has not been evaluated. Because vilazodone is highly bound to plasma protein, administration of VIIBRYD to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects
Pregnancy Category C

Vilazodone caused some developmental toxicity in rats, but was not teratogenic in rats or rabbits. There are no adequate and well-controlled studies of VIIBRYD in pregnant women. When treating pregnant women with VIIBRYD, carefully consider whether the potential benefits outweigh the potential risks of treatment.

No teratogenic effects were observed when vilazodone was given to pregnant rats or rabbits during the period of organogenesis at oral doses up to 200 and 36 mg/kg/day, respectively. These doses are 48 and 17 times, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 40 mg on a mg/m^2 basis. Fetal body weight gain was reduced, and skeletal ossification was delayed in both rats and rabbits at these doses; these effects were not observed at doses up to 10 times the MRHD in rats or 4 times the MRHD in rabbits.

When vilazodone was administered to pregnant rats at an oral dose of 30 times the MRHD during the period of organogenesis and throughout pregnancy and lactation, the number of live born pups was decreased. There was an increase in early postnatal pup mortality, and among surviving pups there was decreased body weight, delayed maturation, and decreased fertility in adulthood. There was some maternal toxicity at this dose. These effects were not seen at 6 times the MRHD.

Nonteratogenic Effects
Neonates exposed to serotonergic antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of serotonergic antidepressants or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome *[see Warnings and Precautions (5.2)]*.

8.2 Labor and Delivery
The effect of VIIBRYD on labor and delivery in humans is unknown. VIIBRYD should be used during labor and delivery only if the potential benefit outweighs the potential risk.

8.3 Nursing Mothers
Vilazodone is excreted into the milk of lactating rats. The effect of VIIBRYD on lactation and nursing in humans is unknown. Breast feeding in women treated with VIIBRYD should be considered only if the potential benefit outweighs the potential risk to the child.

8.4 Pediatric Use
Clinical studies on the use of VIIBRYD in pediatric patients have not been conducted; therefore, the safety and effectiveness of VIIBRYD in the pediatric population have not been established. VIIBRYD is not approved for use in pediatric patients *[see Box Warning and Warnings and Precautions (5.1)]*.

8.5 Geriatric Use
No dose adjustment is recommended on the basis of age (see Figure 2). Results from a single-dose (20 mg) pharmacokinetic study in elderly (> 65 years-old) vs. young (24-55 years-old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups.

Of the 2177 patients in clinical studies with VIIBRYD, 37 (1.7%) were 65 years of age or older, and 272 (12.5%) were 55 to 64 years of age.

Greater sensitivity of some older individuals cannot be ruled out *[see Dosage and Administration (2.3)]*.

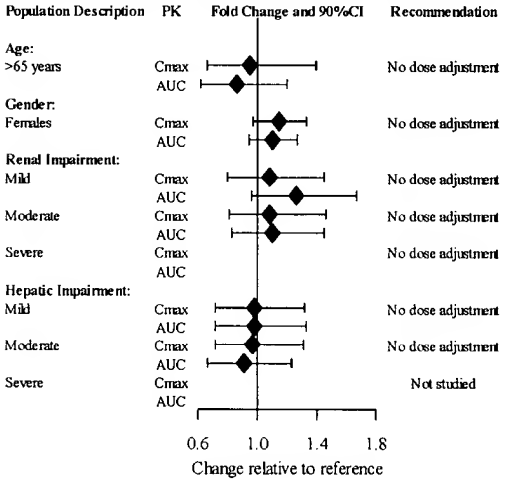
Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions (5.7)]*.

8.6 Hepatic Impairment
Vilazodone is eliminated primarily by hepatic metabolism. In mild and moderate hepatic impairment, no dose adjustment is necessary (see Figure 2). VIIBRYD has not been studied in patients with severe hepatic impairment *[see Dosage and Administration (2.3)]*.

8.7 Renal Impairment
In mild, moderate, and severe renal impairment, no dose adjustment is necessary (see Figure 2 below) *[see Dosage and Administration (2.3)]*.

8.8 Gender Effect
After adjustment for body weight, the systemic exposures between males and females are similar (see Figure 2).

Figure 2. Impact of Intrinsic Factors on Vilazodone PK



The data shown for elderly subjects (>65 years) are relative to younger subjects (24-55 y
The data shown for female subjects are relative to male subjects.
The data shown for renal and hepatic impairment are relative to subjects with normal renal and hepatic function, respectively.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
VIIBRYD is not a controlled substance.

9.2 Abuse and Dependence
VIIBRYD has been systematically studied in animals and did not demonstrate abuse or dependence potential. While VIIBRYD has not been systematically studied in humans for its potential for abuse, there was no suggested evidence of drug-seeking behavior in the clinical studies. However, it is not possible to predict on the basis of clinical experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of VIIBRYD (e.g., development of tolerance, drug-seeking behavior, increases in dose).

10 OVERDOSAGE

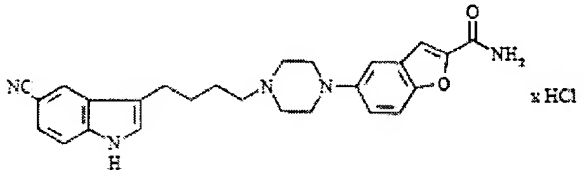
10.1 Human Experience
There is limited clinical experience regarding human overdosage with VIIBRYD. Four patients and 1 patient's child experienced an overdose of VIIBRYD; all recovered. The adverse reactions associated with overdose of VIIBRYD at doses of 200-280 mg as observed in clinical trials included serotonin syndrome, lethargy, restlessness, hallucinations, and disorientation.

10.2 Management of Overdose

Consult a Certified Poison Control Center for up-to-date guidance and advice. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). No specific antidotes for vilazodone are known. In case of an overdose, provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be considered. Removal of vilazodone by dialysis has not been studied; however, the high volume of distribution of vilazodone suggests that dialysis will not be effective in reducing vilazodone plasma concentrations.

11 DESCRIPTION
VIIBRYD Tablets for oral administration contain polymorph Form IV vilazodone hydrochloride (HCl), a selective serotonin reuptake inhibitor and a $5HT_{1A}$ receptor partial agonist.

Vilazodone HCl is 2-benzofurancarboxamide, 5-[4-[4-(5-cyano-1*H*-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1). Its molecular weight is 477.99. The structural formula is:



In addition to the active ingredient, VIIBRYD Tablets contain lactose monohydrate, microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C Blue #1 (40 mg only), FD&C Yellow #6 (20 mg only) and FD&C Red #40 (10 mg only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action
The mechanism of the antidepressant effect of vilazodone is not fully understood but is thought to be related to its enhancement of serotonergic activity in the CNS through selective inhibition of serotonin reuptake. Vilazodone is also a partial agonist at serotonergic $5\text{-}HT_{1A}$ receptors; however, the net result of this action on serotonergic transmission and its role in vilazodone's antidepressant effect are unknown.

12.2 Pharmacodynamics
Vilazodone binds with high affinity to the serotonin reuptake site (Ki= 0.1 nM), but not to the norepinephrine (Ki=56 nM) or dopamine (Ki=37 nM) reuptake sites. Vilazodone potently and selectively inhibits reuptake of serotonin (IC_{50}= 1.6 nM). Vilazodone also binds selectively with high affinity to $5\text{-}HT_{1A}$ receptors (IC_{50}=2.1 nM) and is a $5\text{-}HT_{1A}$ receptor partial agonist.

Thorough QT Study: Treatment with VIIBRYD did not prolong the QTc interval. The effect of vilazodone (20, 40, 60, and 80 mg) on the QTc interval was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg), parallel-group, thorough QTc study in 157 healthy subjects. The study demonstrated an ability to detect small effects. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc interval was below 10 msec, based on the individual correction method (QTcI). This is below the threshold for clinical concern. However, it is unknown whether 80 mg is adequate to represent a high clinical exposure condition.

12.3 Pharmacokinetics
Vilazodone activity is due primarily to the parent drug. The pharmacokinetics of vilazodone (5 mg – 80 mg) are dose-proportional. Accumulation of vilazodone is predictable from single dose data, does not vary with dose, and steady-state is achieved in about 3 days. Elimination of vilazodone is primarily by hepatic metabolism with a terminal half-life of approximately 25 hours. At steady-state, after daily dosing of VIIBRYD 40 mg under fed conditions, the mean C_{max} value is 156 ng/mL, and the mean AUC ($_{0\text{-}24\ hours}$) value is 1645 ng·h/mL.

Absorption
Vilazodone concentrations peak at a median of 4-5 hours (T_{max}) after administration and decline with a terminal half-life of approximately 25 hours. The absolute bioavailability of vilazodone is 72% with food. Administration of VIIBRYD with food (high fat or light meal) increases oral bioavailability (C_{max} increased by approximately 147-160%, and AUC increased by approximately 64-85%).

Coadministration of VIIBRYD with ethanol or with a proton pump inhibitor (pantoprazole) did not affect the rate or extent of vilazodone absorption [*see Drug Interactions (7.3, Figure 1)*]. In addition, neither the T_{max} nor terminal elimination rate of vilazodone was altered by coadministration with either pantoprazole or ethanol.

Absorption is decreased by approximately 25% if vomiting occurs within 7 hours of ingestion; no replacement dose is needed.

Distribution
Vilazodone is widely distributed and approximately 96-99% protein-bound

Metabolism and Elimination
VIIBRYD is extensively metabolized through CYP and non-CYP pathways (possibly by carboxylesterase), with only 1% of the dose recovered in the urine and 2% of the dose recovered in the feces as unchanged vilazodone. CYP3A4 is primarily responsible for its metabolism among CYP pathways, with minor contributions from CYP2C19 and CYP2D6. *In vitro* studies with human microsomes and human hepatocytes indicate that vilazodone is unlikely to inhibit or induce the metabolism of other CYP (except for CYP2C8) substrates; and an *in vivo* study with probe substrates for CYP2C19, 2D6 and 3A4 showed vilazodone did not alter the pharmacokinetics of the probe substrates. However, an *in vivo* study with probe substrate for CYP2C19 demonstrated a minor induction of CYP2C19. Strong inhibitors of CYP3A4 (e.g., ketoconazole) can reduce the metabolism of vilazodone *in vivo* and increase exposure. Conversely, inducers of CYP3A4 can decrease vilazodone exposure *[see Drug Interactions (7.3)]*.

The presence of mild or moderate renal impairment, or mild or moderate hepatic impairment did not affect the apparent clearance of vilazodone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Carcinogenicity studies were conducted in which B6C3F1mice and Wistar rats were given oral doses of vilazodone up to 135 and 150 mg/kg/day, respectively, for 2 years. These doses are approximately 16.5 and 36 times the maximum recommended human dose (MRHD) of 40 mg, respectively, on a mg/m^2 basis.

In mice, the incidence of hepatocellular carcinomas was increased in males at 16.5 times the MRHD; this finding was not observed at 5.5 times the MRHD. The incidence of malignant mammary gland tumors was numerically increased in females at 5.5 and 16.5 times the MRHD, with statistical significance at 16.5 the MHRD; this finding was not observed at 1.8 times the MRHD. Elevated prolactin levels were observed in a 2-week study of vilazodone administered at 5.5 and 33 times the MRHD. Increases in prolactin levels are known to cause mammary tumors in rodents.

In the rat study, vilazodone was not carcinogenic in either sex at doses up to 36 times the MRHD.

Mutagenesis
Vilazodone was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test). Vilazodone was negative in the *in vitro* V79/HGRPT mammalian cell forward mutation assay. Vilazodone was clastogenic in two *in vitro* mammalian cell chromosome aberration assays. However, vilazodone was negative for clastogenic activity in both an *in vivo* rat bone marrow chromosome aberration assay and a micronucleus test. Vilazodone was also negative in an *in vivo/in vitro* unscheduled DNA synthesis assay in rats.

Impairment of Fertility
Treatment of rats with vilazodone at a dose of 125 mg/kg, which is 30 times the maximum recommended human dose (MRHD) of 40 mg on a mg/m^2 basis, caused impairment of male fertility with no effect on female fertility. Impaired male fertility was not observed at 6 times the MRHD.

14 CLINICAL STUDIES
The efficacy of VIIBRYD as a treatment for major depressive disorder was established in two 8-week, multicenter, randomized, double-blind, placebo-controlled studies in adult (18-70 years of age) outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for MDD. In these studies, patients were titrated over 2 weeks to a dose of 40 mg of VIIBRYD with food (n=436) or placebo (n = 433) once daily. VIIBRYD was superior to placebo in the improvement of depressive symptoms as measured by the mean change from baseline to Week 8 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. Examination of population subgroups based on age (there were few patients over 65), gender, and race did not reveal any clear evidence of differential responsiveness.

Table 4. Summary of Results for the Primary Efficacy Endpoint

Study Number	Primary Endpoint	LS Mean (95% CI)[a] difference from placebo in change from baseline
1	MADRS	-3.2 (-5.2, -1.3)
2	MADRS	-2.5 (-4.4, -0.6)

[a] Least Squares Mean (95% Confidence Interval)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
VIIBRYD (vilazodone HCl) Tablets are supplied in the following configurations:

10 mg, pink, oval tablet, debossed with 10 on one side
75838-110-30: 30-count bottles
75838-110-90: 90-count bottles
75838-110-52: 500-count bottles
75838-110-12: 10 blisters cards each containing 10 tablets (HUD)

20 mg, orange, oval tablet, debossed with 20 on one side
75838-120-30: 30-count bottles
75838-120-90: 90-count bottles

75838-120-52: 500-count bottles
75838-120-12: 10 blisters cards each containing 10 tablets (HUD)

40 mg, blue, oval tablet, debossed with 40 on one side
75838-140-30: 30-count bottles
75838-140-90: 90-count bottles
75838-140-52: 500-count bottles
75838-140-12: 10 blisters cards each containing 10 tablets (HUD)

Patient Starter Kit
75838-179-30: blister card containing 30 tablets:
10 mg, pink, oval, debossed with 10 on one side: 7 tablets
20 mg, orange, oval, debossed with 20 on one side: 7 tablets
40 mg, blue, oval, debossed with 40 on one side: 16 tablets

16.2 Storage
VIIBRYD (vilazodone HCl) Tablets should be stored at 25°C (77°F) with excursions permitted to 15°C - 30°C (59°F - 86°F) [*see USP Controlled Room Temperature*].

17 PATIENT COUNSELING INFORMATION
See Medication Guide (17.2).

17.1 Information for Patients
Advise patients and their caregivers about the benefits and risks associated with treatment with VIIBRYD and counsel them in its appropriate use. Advise patients and their caregivers to read the Medication Guide and assist them in understanding its contents. The complete text of the Medication Guide is reprinted at the end of this document.

Suicide Risk
Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dose is adjusted up or down [*see Box Warning and Warnings and Precautions (5.1)*].

Dosing and Administration
Instruct patients to take VIIBRYD with food. When initiating treatment with VIIBRYD the dose should be titrated, starting with a dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then increased to 40 mg once daily.

Concomitant Medication
Instruct patients not to take VIIBRYD with an MAOI or within 14 days of stopping an MAOI and to allow 14 days after stopping VIIBRYD before starting an MAOI [*see Contraindications (4.1)*].

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions
Caution patients about the risk of serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions, particularly with the concomitant use of VIIBRYD and triptans, tramadol, tryptophan supplements, other serotonergic agents, or antipsychotic drugs [*see Warnings and Precautions (5.2) and Drug Interactions (7.1)*].

Seizures
Caution patients about using VIIBRYD if they have a history of a seizure disorder [*see Warnings and Precautions (5.3)*]. Patients with a history of seizures were excluded from clinical studies.

Abnormal Bleeding
Caution patients about the concomitant use of VIIBRYD and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of abnormal bleeding [*see Warnings and Precautions (5.4)*].

Activation of Mania/Hypomania
Advise patients and their caregivers to observe for signs of activation of mania/hypomania [*see Warnings and Precautions (5.5)*].

Discontinuation
Advise patients not to stop taking VIIBRYD without talking first with their healthcare provider. Patients should be aware that discontinuation effects may occur when suddenly stopping VIIBRYD [*see Warnings and Precautions (5.6)*].

Hyponatremia
Advise patients that if they are treated with diuretics, or are otherwise volume depleted, or are elderly, they may be at greater risk of developing hyponatremia while taking VIIBRYD [*see Warnings and Precautions (5.7)*].

Alcohol
Advise patients to avoid alcohol while taking VIIBRYD [*see Drug Interactions (7.3)*].

Allergic Reactions
Advise patients to notify their healthcare provider if they develop an allergic reaction such as rash, hives, swelling, or difficulty breathing.

Pregnancy
Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy with VIIBRYD [*see Use in Specific Populations (8.1)*].

Nursing Mothers
Advise patients to notify their healthcare provider if they are breastfeeding an infant and would like to continue or start VIIBRYD [*see Use in Specific Populations (8.3)*].

Interference with Cognitive and Motor Performance

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that VIIBRYD therapy does not adversely affect their ability to engage in such activities.

TROVIS PHARMACEUTICALS

Distributed by
Trovis Pharmaceuticals LLC
New Haven, CT 06511

877-878-7200
viibryd.com

Licensed from Merck KGaA,
Darmstadt, Germany

Product protected by U.S. Patent No. 5,532,241 and U.S. Patent No. 7,834,020.

VZ59PI0000
Revised: January 2010

MEDICATION GUIDE

VIIBRYD *[vi-brid]*
(vilazodone hydrochloride)
Tablets

Read this Medication Guide carefully before you start taking VIIBRYD and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about VIIBRYD?

VIIBRYD and other antidepressant medicines may cause serious side effects.

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if there is an emergency:

1. Suicidal thoughts or actions:
- **VIIBRYD and other antidepressant medicines may increase suicidal thoughts or actions** in some children, teenagers, or young adults within the **first few months of treatment or when the dose is changed.**
- Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions.
- Watch for these changes and call your healthcare provider right away if you notice:
- New or sudden changes in mood, behavior, actions, thoughts, or feelings, especially if severe.
- Pay particular attention to such changes when VIIBRYD is started or when the dose is changed.

  Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.

  Call your healthcare provider right away if you have any of the following symptoms, especially if they are new, worse, or worry you:
  - attempts to commit suicide
  - acting on dangerous impulses
  - acting aggressive or violent
  - thoughts about suicide or dying
  - new or worse depression
  - new or worse anxiety or panic attacks
  - feeling agitated, restless, angry or irritable
  - trouble sleeping
  - an increase in activity or talking more than what is normal for you (mania)
  - other unusual changes in behavior or mood

2. Serotonin Syndrome or Neuroleptic Malignant Syndrome-like reactions:
- agitation, hallucinations, coma or other changes in mental status
- coordination problems or muscle twitching (overactive reflexes)
- fast heartbeat, high or low blood pressure
- sweating or fever
- nausea, vomiting, or diarrhea
- muscle stiffness or tightness

3. Abnormal bleeding: VIIBRYD and other antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin, Jantoven), a non-steroidal anti-inflammatory drug (NSAID), or aspirin.

4. Seizures or convulsions.

5. Manic episodes:
- greatly increased energy
- severe trouble sleeping
- racing thoughts
- reckless behavior
- unusually grand ideas
- excessive happiness or irritability
- talking more or faster than usual

6. Low salt (sodium) levels in the blood.

Elderly people may be at greater risk for this. Symptoms may include:

- headache
- weakness or feeling unsteady
- confusion, problems concentrating or thinking or memory problems

Do not stop VIIBRYD without first talking to your healthcare provider. Stopping VIIBRYD suddenly may cause serious symptoms including:

- anxiety, irritability, high or low mood, feeling restless or sleepy
- headache, sweating, nausea, dizziness
- electric shock-like sensations, tremor, confusion

What is VIIBRYD?

VIIBRYD is a prescription medicine used to treat a certain type of depression called Major Depressive Disorder (MDD). It is important to talk with your healthcare provider about the risks of treating depression and also the risk of not treating it. You should discuss all treatment choices with your healthcare provider.

Talk to your healthcare provider if you do not think that your condition is getting better with VIIBRYD treatment.

It is not known if VIIBRYD is safe and effective in children.

Who should not take VIIBRYD?

Do not take VIIBRYD if you:

- Take an Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI.
  - Do not take an MAOI within 14 days of stopping VIIBRYD.
  - Do not start VIIBRYD if you stopped taking an MAOI in the last 14 days.

  People who take VIIBRYD close in time to taking an MAOI may have serious or even life-threatening side effects. Get medical help right away if you have any of these symptoms:
  - high fever
  - uncontrolled muscle spasms
  - stiff muscles
  - rapid changes in heart rate or blood pressure
  - confusion
  - loss of consciousness (pass out)

What should I tell my healthcare provider before taking VIIBRYD?

Before starting VIIBRYD, tell your healthcare provider if you:

- have liver problems
- have kidney problems
- have or had seizures or convulsions
- have bipolar disorder (manic depression) or mania
- have low sodium levels in your blood
- have or had bleeding problems
- drink alcohol
- have any other medical conditions
- Are pregnant or plan to become pregnant. It is not known if VIIBRYD will harm your unborn baby. Talk to your healthcare provider about the benefits and risks of treating depression during pregnancy.
- Are breastfeeding or plan to breastfeed. It is not known if VIIBRYD passes into breast milk. You and your healthcare provider should decide if you should take VIIBRYD while breastfeeding.

Tell your healthcare provider about all the medicines that you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. VIIBRYD and some medicines may interact with each other, may not work as well, or may cause serious side effects when taken together.

Especially tell your healthcare provider if you take:

- triptans used to treat migraine headache
- medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, SSRIs, SNRIs, buspirone, or antipsychotics
- tramadol
- over-the-counter supplements such as tryptophan or St. John's Wort
- nonsteroidal anti-inflammatory drugs (NSAIDS)
- aspirin

- warfarin (Coumadin, Jantoven)
- mephenytoin (Mesantoin)
- diuretics

Your healthcare provider or pharmacist can tell you if it is safe to take VIIBRYD with your other medicines. Do not start or stop any medicine while taking VIIBRYD without talking to your healthcare provider first.

How should I take VIIBRYD?

- Take VIIBRYD exactly as prescribed. Your healthcare provider may need to change the dose of VIIBRYD until it is the right dose for you.
- **Take VIIBRYD with food.** VIIBRYD may not work as well if you take it on an empty stomach.
- If you miss a dose of VIIBRYD, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of VIIBRYD at the same.
- If you take too much VIIBRYD, call your healthcare provider or poison control center right away, or get emergency treatment.

What should I avoid while taking VIIBRYD?

- VIIBRYD can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how VIIBRYD affects you.
- You should avoid drinking alcohol while taking VIIBRYD. See "What should I tell my healthcare provider before taking VIIBRYD?"

What are the possible side effects of VIIBRYD?

VIIBRYD may cause serious side effects, including:

- **See "What is the most important information I should know about VIIBRYD?"**

Common side effects in people who take VIIBRYD include:

- diarrhea
- nausea or vomiting
- trouble sleeping

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of VIIBRYD. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VIIBRYD?

Store VIIBRYD at room temperature (59°F to 86°F or 15°C to 30°C).

Keep VIIBRYD and all medicines out of the reach of children.

General information about VIIBRYD.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VIIBRYD for a condition for which it was not prescribed. Do not give VIIBRYD to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about VIIBRYD. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about VIIBRYD that is written for healthcare professionals.

For more information about VIIBRYD call 1-877-878-7200 or go to www.VIIBRYD.com.

What are the ingredients in VIIBRYD?

Active ingredient: vilazodone hydrochloride
Inactive ingredients: lactose monohydrate, microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and FD&C Blue #1 (40 mg only), FD&C Yellow #6 (20 mg only) and FD&C Red #40 (10 mg only).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

TROVIS PHARMACEUTICALS

Trovis Pharmaceuticals LLC
5 Science Park
New Haven, CT 06511

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Product protected by U.S. Patent No. 5,532,241 and U.S. Patent No. 7,834

VIIBRYD™ is a trademark of Trovis Pharmaceuticals LLC.

Revised January2011

NDA 22-567 vilazodone HCl Tablets

Viibryd™

(*vilazodone hydrochloride*)

Class of Product: Antidepressant

PGxHealth, LLC
5 Science Park
New Haven, CT 06511

Contact Information: PGxHealth, LLC (1-877-878-7200)

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of this REMS is to inform patients about the serious risks associated with the use of vilazodone HCl Tablets.

II. REMS ELEMENTS:

A. Medication Guide

PGxHealth, LLC, will ensure that a currently approved Medication Guide will be dispensed with each vilazodone prescription in accordance with 21 CFR 208.24.

B. Timetable for Submission of Assessments

PGxHealth, LLC, will submit REMS Assessments to FDA at 18 months, 3 years, and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. PGxHealth, LLC will submit each assessment so that it will be received by the FDA on or before the due date.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
01/21/2011

EXHIBIT 7

Certificate of Correction

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,532,241
APPLICATION NO. : 08/314734
DATED : July 2, 1996
INVENTOR(S) : Henning Bottcher et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 16, Line 46, please delete "R^3 is H, OH or OA;"

Signed and Sealed this

Tenth Day of November, 2009

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

EXHIBIT 8

Patent Bibliographic Data

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United States Patent and Trademark Office

Patent Bibliographic Data				02/08/2011 11:26 AM	
Patent Number:	5532241		**Application Number:**	08314734	
Issue Date:	07/02/1996		**Filing Date:**	09/29/1994	
Title:	PIPERIDINES AND PIPERAZINES				
Status:	4th, 8th and 12th year fees paid			**Entity:**	Large
Window Opens:	N/A	**Surcharge Date:**	N/A	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:					
Surcharge Fee Code:					
Most recent events (up to 7):	12/11/2007 12/09/2003 12/29/1999 09/10/1996	Payment of Maintenance Fee, 12th Year, Large Entity. Payment of Maintenance Fee, 8th Year, Large Entity. Payment of Maintenance Fee, 4th Year, Large Entity. Payor Number Assigned. --- End of Maintenance History ---			
Address for fee purposes:	CPA GLOBL LIMITED 2318 Mill Road 12th Floor ALEXANDRIA, VA 22314				

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Patent Number:	5532241	**Application Number:**	08314734
Issue Date:	07/02/1996	**Filing Date:**	09/29/1994
Window Opens:		**Surcharge Date:**	
Window Closes:		**Payment Year:**	
Entity Status:	LARGE		

Customer Number:	197
Street Address:	CPA GLOBL LIMITED
City:	ALEXANDRIA
State:	VA
Zip Code:	22314
Phone Number:	(703) 739-2234

Currently there are no fees due.

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DATE PRINTED
02/08/2011

CPA GLOBL LIMITED
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MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,532,241	**$830.00**	**$0.00**	**12/29/99**	**08/314,734**	**07/02/96**	**09/29/94**	**04**	**NO**	**MERCK1617**

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CPA GLOBL LIMITED
2318 Mill Road 12th Floor
ALEXANDRIA VA 22314

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,532,241	**$2,090.00**	**$0.00**	**12/09/03**	**08/314,734**	**07/02/96**	**09/29/94**	**08**	**NO**	**MERCK1617**

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
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PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,532,241	**$3,910.00**	**$0.00**	**12/11/07**	**08/314,734**	**07/02/96**	**09/29/94**	**12**	**NO**	**MERCK1617**

EXHIBIT 9

Letter Acknowledging Receipt of the IND

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 54,613 Date DEC 1 1997

Lipha Pharmaceuticals, Inc.
ATTN: Anita M. Goodman, M.D.
9 West 57th Street, Suite 3825
New York, NY 10019-2701

Dear Sir or Madam:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned:	54,613
Sponsor:	Lipha Pharmaceuticals, Inc.
Name of Drug:	EMD 68 843
Date of Submission:	November 21, 1997
Date of Receipt:	November 24, 1997

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations). Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon as possible and in no event later than 10 working days after initial receipt of the information and reporting any unexpected fatal or life-threatening experience to the FDA by telephone no later than 3 working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this IND, please contact: Mr. Paul David
Project Manager
(301) 594-2777

Sincerely yours,

John Purvis
Chief, Project Management Staff
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Original IND - pink
HFD-120 - yellow
HFD-120/CSO - green

IND ACKNOWLEDGEMENT

EXHIBIT 10

Letter Acknowledging Receipt of NDA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-567

NDA ACKNOWLEDGMENT

PgxHealth, LLC
Attention: Kimberly Fabrizio
Vice President, Regulatory Affairs
Five Science Park
New Haven, CT 06511

Dear Ms. Fabrizio:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Vilazodone HCL tablets, 10 mg, 20 mg, and 40 mg

Date of Application: March 22, 2010

Date of Receipt: March 22, 2010

Our Reference Number: NDA 22-567

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 21, 2010 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm

If you have any questions, call me at (301) 796-2145.

Sincerely,

{See appended electronic signature page}

CDR Bill Bender, R.Ph., MS HCA
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22567	ORIG-1	PGX HEALTH LLC	VILAZODONE HCL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H BENDER
03/24/2010

EXHIBIT 11

List of Significant Activities Undertaken during Regulatory Review Period

LIST OF SIGNIFICANT ACTIVITIES UNDERTAKEN DURING THE REGULATORY REVIEW PERIOD

SUBMISSION DATE	SERIAL NUMBER	DESCRIPTION
11/21/1997	000	IND Submitted to FDA (IND Effective on December 21, 1997)
2/27/1998	004	Draft Rat and Mouse Carcinogenicity Study Protocols for CAC review
8/26/1998	007	Transfer of IND Ownership from Lipha Pharmaceuticals to Merck KGaA
12/1/1998	010	Study Protocol - 15-Day Safety Report
12/31/1998	011	Study Protocol - 15-Day Safety Report
3/5/1999	013	Annual Report 1998 (12 volumes)
6/16/1999	014	Study Protocol - Protocol Amendment
2/21/2000	018	Annual Report 1999 (6 volumes)
12/19/2000	020	FDA Correspondence (toxicology)
2/8/2001	021	Annual Report 2000 (4 volumes)
4/30/2001	022	Submission of Phase 2 Study Reports
1/5/2001	023	Transfer of IND Ownership to GSK
5/15/2001		FDA Correspondence (Clinical)
10/25/2001	027	Protocol Amendment
12/21/2001	032	Protocol Amendment
3/1/2002	037	Protocol Amendment
4/30/2002	039	Protocol Amendment
7/24/2002	044	Protocol Amendment
10/23/2002	047	General Correspondence (Protocol)
1/7/2003	050	Protocol Amendment
2/11/2003	052	Transfer of IND Ownership to Merck KGaA
11/7/2003	053	Information Amendment - General Correspondence
2/20/2004	054	General Correspondence
10/25/2004	055	Transfer of IND Ownership to GNSC
12/22/2004	057	Submission of Carcinogenicity Report
1/19/2005	058	Annual Report 2004
1/5/2005		General Teleconference (FDA) - Outstanding Reports
5/12/2005		FDA Correspondence (Pharm/Tox))
10/10/2005		FDA Type B Meeting Request (End-of-Phase 2 meeting)
11/19/2005	060	FDA Meeting Request Briefing Documents
12/21/2005	061	Protocol Submission
6/22/2006	065	FDA Meeting Request (CMC and Clin Pharm)
7/6/2006	067	FDA Meeting Request Briefing Documents

SUBMISSION DATE	SERIAL NUMBER	DESCRIPTION
1/17/2007	069	Annual Report 2006
3/26/2007	071	Clinical Statistical Analysis Plan
7/20/2007	074	Responses to FDA SAP Comments
8/3/2007		General Correspondence (Drug Substance)
9/27/2007	077	Protocol Submission
1/8/2008	080	Investigator Brochure and Protocol
4/25/2008	091	IND Safety Report
6/8/2008	095	IND Safety Report
8/1/2008	100	Clinical Study Report
10/20/2008	109	Clinical Study Report
12/8/2008	116	Clinical Study Report
1/19/2009	123	Annual Report (2008)
3/11/2009	128	IND Safety Report
6/3/2009	134	CMC Update/Amendment
8/19/2009		FDA Contact Report
1/14/2010		FDA Contact Report
1/24/2010	142	Annual Report (2009)
3/22/2010		NDA No. 22-567 Submission
1/21/2011		NDA No. 22-567 FDA Approval